Subconceptual Processing in Medicine: From Body & Mind to Health & Healing

PhD Thesis

towards the title of 'Doctor of Medical Science'

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We should not doubt whether psyche and body are one thing, any more than whether the wax and its imprint are, or in general whether the matter of each thing is one with that of which it is the matter." [Aristotle, De Anima]

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Abbreviations

ANN: Artificial Neural Networks

AI: Artificial Intelligence

PDP: Parallel Distributed Processing

SP: Subconceptual Processing

1 Summary

Subconceptual processing lies at a level above that of biochemistry, and yet *anatomically* below the level of distinct central nervous system structures, as well as *conceptually* below the level of concepts themselves. It is the level where neurons form patterns, with many of them participating in each pattern. These patterns in turn are distributed within the brain, work in parallel and overlap with each other. It is the level where the brain and mind appear unified, a single entity with two different aspects. This view is congruent with insights from *cognitive neuroscience* and *artificial neural networks*.

Subconceptual processing provides a parsimonious explanation for phenomena such as empathy and the placebo effect, and sheds light on areas such as medical causal thinking, evidence-based medicine, and psycho-somatics in general. It has important consequences for many medical conditions, including chronic pain, peptic ulcer disease, myocardial ischemia and epilepsy. We have delved into these domains and shown how the concept of subconceptual processing can enhance our understanding, providing many insights that are consistent with established data. Through future research, this understanding may lead to ways of managing many conditions, including through hygienic measures. What we have discovered is all the more important, since, despite many years of research, biochemical and other materialist hypotheses about psycho-somatics and psychopathological conditions such as depression, schizophrenia and ADD are lacking or incomplete.

Through an examination of double-blind procedures as well as medical causal thinking, we conclude that proper theoretical analysis deserves a much more prominent role in medical thinking, as compared to the almost exclusive importance given to empirical knowledge today. This theoretical analysis should be consistent with the wealth of facts that have arisen from the neuronal domain. In many cases, the results of this may be disruptive, but they will benefit science, as well as the health and well-being of many people.

This thesis permanently brings together body and mind in the domain of health and healing. It provides a way for us to understand, investigate and communicate about a unified body and mind. Many people talk about mind/body unity, but they do not act on the concept – or see the mind and brain as two different parts within a larger whole. Now, body and mind can be seen scientifically as wax and imprint, as paint and the artistic painting. Without paint, there is no art, and yet it is the art that is most important – without art, paint has no meaning.

Subconceptual processing is also the level of deeper meanings – what things really mean and how they can 'touch' someone, such as a belief that pervades the core of their being. As such, it is also the level of poetry and of 'subconceptual communication' – communication with the deeper layers of the mind. The result of this is not cold materialism, but instead a synthesis of rationalism and humanity that is completely warm.

We hope that this synthesis will become central to future healthcare. It will have enormous consequences for psychotherapy, CAM, medical epistemology, medical ethics, and many other areas. It will create sustainability and huge cost savings at many levels, while providing new ways of enhancing the health of individuals and of society. The patient will become more central - not only will we organize healthcare around them, we will also view them as an important source of their own health: the ‘patient as cure’.

1 Samenvatting

Subconceptual processing situeert zich op een niveau boven dat van biochemie en tevens *anatomisch* onder het niveau van afzonderlijke structuren van het centraal zenuwstelsel, zowel als *conceptueel* onder het niveau van concepten zelf. Het is het niveau waarop neuronen patronen vormen, waarbij aan elk afzonderlijk patroon veel neuronen deelnemen. Deze patronen liggen op hun beurt verspreid binnen de hersenen, werken in parallel en overlappen met elkaar. Het is het niveau waarop hersenen en geest een eenheid vormen, één entiteit met twee verschillende aspecten. Dit beeld is congruent met inzichten van cognitieve neurowetenschappen en artificiële neurale netwerken.

Subconceptual processing biedt een éénduidige verklaring voor fenomenen als empathie en het placeboeffect, en werpt licht op gebieden zoals medisch oorzakelijk denken, evidence based medicine, en psychosomatiek in het algemeen. Het heeft belangrijke gevolgen voor veel medische condities zoals chronische pijn, peptisch ulcus, myocard ischemie en epilepsie. Wij hebben binnen deze domeinen aangetoond hoe het concept van subconceptual processing kan leiden tot veel inzichten die consistent zijn met gevestigde feiten. Door middel van toekomstig onderzoek kan dit begrip leiden tot manieren om veel medische condities te behandelen, inclusief met hygiënische maatregelen. Dit is des te belangrijker omdat ondanks vele jaren van onderzoek biochemische en andere materialistische hypothesen over psychosomatiek en psychopathologische condities zoals depressie, schizofrenie en ADD nog steeds ontbreken of onvolledig zijn.

Door onderzoek van dubbelblind procedures en van medisch oorzakelijk denken besluiten wij dat een goede manier tot theoretische analyse een veel prominentere rol in het medische denken verdient, in vergelijking met het bijna exclusieve belang dat momenteel gehecht wordt aan empirische kennis. Deze theoretische analyse dient verenigbaar te zijn met de vele feiten uit het neuronale domein. In veel gevallen kunnen de resultaten hiervan disruptief (domein-verstorend) zijn, maar zij zullen leiden tot betere wetenschap en de gezondheid en het welzijn van velen ten goede komen.

Deze thesis brengt voor altijd lichaam en geest samen. Ze bekrachtigt een manier om geest-lichaam eenheid te begrijpen, te onderzoeken en erover te

communiceren. Velen praten over geest/lichaam eenheid, maar zij handelen niet volgens het concept – of ze zien geest en hersenen als twee verschillende delen binnen een groter geheel. Nu kunnen lichaam en geest wetenschappelijk worden gezien als was en afdruk, als verf en kunst. Zonder verf is er geen kunst, en toch is de kunst het belangrijkste. Zonder kunst heeft de verf geen betekenis.

Subconceptual processing is ook het niveau van diepere betekenissen – wat dingen werkelijk betekenen en hoe zij iemand kunnen ‘raken', zoals een geloof dat de kern van het zijn doordringt. Als dusdanig is het ook het niveau van poëzie en van 'subconceptuale communicatie’ – communicatie met de diepere lagen van de geest. Het resultaat hiervan is geen koud materialisme maar in de plaats daarvan een synthese van rationaliteit en warme humaniteit.

Wij hopen dat deze synthese centraal zal staan in de toekomstige gezondheidszorg. Dit zal enorme gevolgen hebben voor psychotherapie, CAM, medische epistemologie, medische ethiek, en veel andere gebieden. Het zal tot verhoogde duurzaamheid leiden en tot grote kostenbesparingen op vele niveaus. Het zal nieuwe manieren creëren om de gezondheid van individuen en van de maatschappij te verbeteren. De patiënt zal centraler staan. Niet alleen zal de gezondheidszorg rond de patiënt georganiseerd worden; de patiënt zelf zal ook gezien worden als belangrijke bron van eigen gezondheid: de ‘patiënt als geneesmiddel’.

General Scheme

Subconceptual Processing
and the Concept of Deeper Meaning
(an introduction)

⇩

Implications on Broad Domains
Basic Question: 'Cloud or Clock?'
Placebo (3 articles)
Empathy
What Works Towards *What*?
Causal Thinking in Medicine
Evidence Based Medicine

⇩

Implications on Some Specific Domains
MPH Effect on Cognitive Function of Students
Epilepsy & Psychogenic Non-Epileptic Seizures
Peptic Ulcer Disease & Functional Dyspepsia
Myocardial Ischemia
Chronic Pain (1 article, 2 congress entries)

⇩

Broader Discussion of Subconceptual Processing

⇩

Discussion of Subconceptual Processing in Medicine

⇩

SWOT, General Conclusions and Perspectives

2 Introduction

> *"Our soul and body are so linked that once we have joined some bodily action with a certain thought, the one does not occur afterwards without the other occurring too…"* [from Descartes, 'The Passions of the Soul', 1649]

2.1 About Concepts

When talking about the 'subconceptual', it is also important to understand what is meant by 'conceptual'. This is not a straightforward discussion. According to the classical view of concepts, the definition of a concept is "*a proposition that gives a set of individually necessary and jointly sufficient conditions for being in the possible-worlds extension of the concept being analyzed.*" [Internet Encyclopedia of Philosophy, IEP, http://www.iep.utm.edu/concepts]

This classical theory provides a profound grounding for the kind of philosophical inquiry that began with Socrates, searching for answers to questions of the type "*What is x*?" – where *'x'* is the nature of knowledge, the mind, or other similar entities. This presupposes that there is such a thing as the nature of knowledge or the nature of the mind, and also assumes that there are legitimate answers to such questions. However, several objections have been raised to this classical theory, including the following:

- '*Plato's problem*': few – if any – classical analyses have ever been widely accepted, except in the case of logic and mathematics. In particular, no philosophically interesting concepts such as knowledge, justice and freedom

of action have been analyzed successfully to date despite more than 2000 years of philosophical inquiry.

- *Vagueness*: given the existence of all necessary and jointly sufficient conditions, a classical analysis would logically lead to a precise extension of the concept being analyzed (in other words, for all *x*, *x* is either definitely or definitely not in the extension of C). This is seldom true. Terms such as 'bleak', 'healthy' and 'myocardial infarction' all have cases where it is unclear whether the term applies. In other words, the concepts expressed by these terms have vague extensions and no precise boundaries.

- *Problems involving typicality effects*: humans sort at different speeds and at different levels of reliability depending on the typicality of the objects being sorted. For instance, swallows are more readily sorted into the *bird* category than are penguins or ostriches.

Today, there are several competing views of conceptuality. These include the prototype theory of concepts (where agents employ lists of typical but non-defining features), and the exemplar theory of concepts (where agents employ a representation of a paradigmatic or most exemplary instance of a concept).

In our view, this problem can be satisfactorily resolved by treating 'concept' itself as a term with two distinct meanings depending on the point of view taken. Concepts are either entities that exist in the mind – or at least depend on it – or they exist independently of the mind. This latter independent formulation is the Platonic view to which classical theory applies. Therefore, there are no discussions that involve a single definition of 'concept', but instead discussions that use a single term to represent two very different things.

The objections listed above are objections to the Platonic view of concepts. However, this thesis does not deal with this Platonic view – instead, it addresses concepts that depend on the mind. In fact, the objections to the classical view simply serve to remind us that Platonic concepts have little place when talking about concepts that exist within or depend on the mind. When addressing mental concepts, it is natural to go 'beyond concepts'. Even when thinking conceptually, we naturally live and think in a more subconceptual way than is evident at first glance. The prototype and exemplar definitions of concepts offer no refuge, since if

concepts such as for 'defining features' are introduced into the definition of concepts, the same objections apply.

2.2 About 'Subconceptual'

> *Subconceptual processing (SP) deals with the way that we perform any mental action as seen in fine detail. Small elements (neurons, dendrites, synapses…) in our brain act together to form patterns of activity that make up how we feel, think and are motivated. In contrast to a semantic network where different nodes represent concepts, the distinct elements within a subconceptual neural/neuronal network do not. Instead of equating to a mentally accessible concept, each node represents something smaller. A mentally accessible concept arises through the interplay of many of these subconceptual nodes within a distinct pattern. Each node in turn participates in multiple patterns, and therefore in multiple concepts.*

SP theory holds that this level determines what we think and is thus also necessary towards an in-depth understanding of human mind, stating that: "*in the dichotomy of conceptual and subconceptual processes may lie the key to achieving the fundamental understanding of the architecture of cognition and intelligence… it is also important to address the problem of modeling both types of processes (conceptual and subconceptual) in an integrated architecture, in order to strive for a better understanding of the overall cognitive architecture."* (Ron Sun, 1994, p.10-11) In neuronal networks, this is the case not only at basic sensory levels but also at higher levels of cognition: "*Nervous systems… are vast networks of networks, with various regions specializing for various tasks. This is evident in sensory systems, such as the visual system, the olfactory system, and so on, but it seems also true of functions more highly cognitive, such as speech production, speech comprehension, planning, and conforming to social conventions."* (Churchland & Sejnowski, 1992, p.317)

To understand SP, the level of the individual neuron is necessary but not enough: "*Networks of neurons in the cerebral cortex generate complex outputs that are not simply predicted by their inputs. These emergent responses underlie the function of*

the cortex. Understanding how cortical networks carry out such transformations requires a description of the responses of individual neurons and of their networks at multiple levels of analysis." (Schummers, Mariño & Sur, 2004, p.430) Mental representations are cast in the substrate of neural distributed patterns in at least 2 ways: "*Sometimes 'representation' refers to cognitive events happening now, such as a visual perception; other times it refers to the capacity (not now exercised) to have appropriate cognitive events, such as my capacity to recognize an osprey. Patterns of activity in networks hook up with the first sense; configurations of connection weights (which yield the appropriate patterns of activity when given specific inputs) hook up with the second sense. Think of the first as displaying knowledge and the second as the enduring structure, or background conceptual framework, that makes the current display possible."* (Churchland, 2002, p.296) Patterns and pattern recognition are central. The brain even repeatedly performs a lot of pattern recognition on its own previously formed patterns, towards always more abstract levels: "*pattern recognition plays a fundamental role at all levels of processing, from sensation through reasoning… from an intensity pattern to a set of objects in three-dimensional space, from a sound pattern to a sequence of words, from a sequence of words to a semantic description, from a set of patient symptoms to a set of disease states, from a set of givens in a physics problem to a set of unknowns. Each of these processes is viewed as completing an internal representation of a static state of an external world. By suitably abstracting the task of interpreting a static sensory input, we can arrive at a theory of interpretation of static input generally… that applies to many cognitive phenomena in the gulf between perception and logical reasoning."* (Bechtel & Abrahamsen, 2002, p.103)

Since the distinct elements within a subconceptual network contribute to the formation of conceptual mental entities but are not themselves conceptual, the processing that they carry out can rightly be called subconceptual processing. However, the term SP has seldom been used in the literature. Terms such as subconceptual *level*, *knowledge* or *representation* are more common. The term *subconceptual processing* is preferred in this thesis because in the human – or animal – brain, everything is dynamic. This is one of the main differences between animal brains and computers. Furthermore, it is likely that the dynamic nature of our brains is an essential characteristic that makes us what we are. There are continuously changing patterns, with change happening at several levels simultaneously: "*Neurons are highly specialized structures, are resistant to change, but are engaged in distributed neural networks that do dynamically change over the*

lifespan. Changes in functional connectivity, for example by shifts in synaptic strength, can be followed by more stable structural changes. Therefore, the brain is continuously undergoing plastic remodeling… Dynamically changing neural networks might thus be considered evolution's invention to enable the nervous system to escape the restrictions of its own genome (and its highly specialized cellular specification) and adapt fluidly and promptly to environmental pressures, physiological changes and experiences. Therefore, representations of function in the brain may be best conceptualized by the notion of distributed neural networks… [Inputs to nodes] shift depending on the integration of a node in a distributed neural network, and the layered and reticular structure of the cortex with rich reafferent loops provides the substrate for rapid modulation of the engaged network nodes." (Alvaro Pascual-Leone, 2009, p.141)

In the face of pattern recognition at multiple levels on the fly, we may also better understand how distinct thoughts do not appear in our head instantaneously and unconnectedly 'as by magic', but instead develop over a number of milliseconds – during which time they can be influenced by many other patterns at the subconceptual level. Put bluntly, conscious conceptual thinking may only offer hindsight of what has already occurred at the subconceptual level. Therefore also and as a natural side-effect, we actually never think the same thought twice.

Although neurotransmitters and biochemistry as a whole play a major role in brain function, SP is not specifically about this: "*Mental states are not represented by molecules alone, or even by a mix of molecules. As we've seen, they are instead accounted for by intricate patterns of information processing within and between synaptically connected neural circuits. Chemicals participate in synaptic transmission, and in the regulation or modulation of transmission, but it is the pattern of transmission in circuits, more than the particular chemicals involved, that determines the mental state."* (LeDoux, 2002, p.261) SP is the 'higher level' that lies between biochemistry and the aspects of the human mind that we can perceive both introspectively and behaviorally. Relevant questions within SP are ones such as "How do we actually perform acts such as seeing, thinking, paying attention, being empathic and even being conscious?" The answers are couched in terms of neuronal structure, and into large and small neuronal patterns within our mind/brain. This is not the 'where' question – which regions of the brain carry out specific processes and which regions cooperate – but instead asks 'how'.

Taking this approach, SP may evolve from the 'bottom up' to address domains that have historically been disconnected from the neuronal domain. Psychology, philosophy, education and leadership are just a few of the domains that may be brought in scope. In several of these areas, there is a growing awareness of this connection. Curiously however, although medicine is intimately entwined with the mind/brain, there has been little progress in elucidating the nature of this connection. One major reason for this may be the fact that modern medical thinking and practice is largely based on the Cartesian model of mind/brain dualism that arose a few centuries ago – without acknowledging the role of SP, the mind and body appear as two separate entities. Descartes made the assumptions 1) that the mind (soul) and body are completely distinct, and 2) that through introspection, one can know everything that is present in one's mind with certainty – and these views still often prevail. However, this difference between the *physical* and the *psychological* exists only in the eye of the beholder.

Contrary to the Cartesian view, SP provides a unified picture of the mind and body, where neuronal patterns – made up of simple non-conceptual neuronal and synaptic nodes that act together physically – give rise to psychological phenomena such as thoughts, feelings, and motivations. The difference between the *physical* and *psychological* level becomes arbitrary, and there is no such thing as the body influencing the mind and vice versa – both are the same thing, although described in different terms. SP thus provides a concrete and scientific approach to overcoming Cartesian dualism - it is a pragmatic missing link between the mind and brain. It is not, however, a cold reduction of mind to matter, but instead represents an overlap where deeper meaning is imprinted on a concrete substrate. Meaning is not relativized away, but instead is greatly enhanced in value. This view has the potential to give medical practitioners deeper insights into pathogenesis, and to deliver relevant cures for many conditions.

SP is also related to the domain of artificial neural networks (ANN), a field of artificial intelligence (AI) that is inspired by human neuronal networks. Here, researchers have been able to develop computational models for neuronal theories, such as coarse coding, automatic generalization and pattern recognition, and embed them in a computerized environment. This has enabled us to explore and better understand theoretical neuronal constructs, both giving insights into the workings of the human mind/brain and furthering the field of AI. Terms related to SP preferentially used by AI researchers are parallel distributed processing (PDP) and

connectionism. Historically seen, "a*t the same time that computational neuroscience was moving beyond its roots in the first wave of neural network models, a second wave of researchers from cognitive psychology and AI adopted neural networks as a medium for modeling human cognition. This intersection of two previously distinct trajectories in the early 1980s produced the distinctive approach to network modeling known as connectionism. The primary goal was to achieve a deeper, more complete account of cognition than had been obtained from the rules and symbolic representations of the information processing framework. Both neural plausibility and computational power were attractive to connectionists, but primarily as means to the end of modeling and understanding cognition."* (Bechtel & Abrahamsen, 2002, p.107)

An additional number of quotations in 'subconceptual' respect are included as an addendum to this thesis. Note that despite extensive thought and research, there is still no explanation as to why the neural basis of an experience is specific to that experience, rather than to another one or to none at all. Further research is needed to bridge this gap, and will require the ability to record the activity of many neurons at the same time.

2.3 Infant Subconceptual Processing

The brains of newborn babies are not fully developed – notably the prefrontal cortex is still in a 'primitive' state. This makes the way that infants learn interesting. On the other hand, it is also important to acknowledge that even at this early stage – and probably within the womb to a significant extent – the subconceptual layers needed for a whole life of conceptual/subconceptual thought are already being established.

Obviously, an infant does not deal with fully formed concepts. It performs basic map making, learning that things that it sees regularly – such as its mother's face – are important. It also learns which relationships between mapped objects are worthy of attention. During this process, a baby naturally performs 'automatic generalization', forming maps that become less fuzzy over time. However, nature does not demand perfection but only what is good enough. "*The brain takes shape. It does this through unconsciously registering the patterns that form when a group of neurons are active simultaneously. (Individual neurons cannot make patterns.) Patterns are formed by the ensemble of neurons as they rise into activity, respond to each other and to*

environmental stimuli, and then fade away, creating a 'cocktail party' of chatter in the brain… Once neurons are formed into patterns, they can be used to organize experience and make interactions with others more predictable. As Daniel Siegel put it, the brain is an 'anticipation machine'. It is designed to help us navigate our way, providing expectations of likely outcomes and holding knowledge of our environment." (Gerhardt, 2004, p.44) The maps that form at these early stages are "*unrememberable yet unforgettable… We cannot consciously recall any of it, yet it is not forgotten because it is built into our organism and informs our expectations and behavior.*" (Gerhardt, 2004, p.15). These early maps form the basic mental landscape that the infant will carry for the rest of its life, serving as the foundation for future maps yet to be constructed. For instance, they provide the basic feeling of trust – or lack of it – that colors all other map-making experiences. In other words, they provide the background coloration for the multidimensional painting that is the adult mind. "*Although later experience will elaborate our responses and add to the repertoire, the path that is trodden in very early life tends to set each of us off in a particular direction that gathers its own momentum.*" (Gerhardt, 2004, p.85)

In an infant, even the concept of 'self' is not developed: "*Babies need a caregiver who identifies with them so strongly that the baby's needs feel like hers; he is still physiologically and psychologically an extension of her.*" (Gerhardt, 2004, p.23) In fact, communication between mother and child also lacks conceptuality: "*Early regulation is also about responding to the baby's feelings in a non-verbal way. The mother does this mainly with her face, her tone of voice, and her touch.*" (Gerhardt, 2004, p.23)

These unconsciously acquired patterns have been described in different ways by various authors. Daniel Stern writes about 'representations of interactions that have been generalized' (RIGs) (Stern, 1985). John Bowlby writes about 'internal working models' (Bowlby, 1969). Wilma Bucci writes about 'emotion schemas' (Bucci, 1997). Robert Clyman writes about 'procedural memory' (Clyman, 1991). However, whatever their specific theory, they all acknowledge that expectations about and of other people are established in the brain from the earliest stages of life onwards. These expectations lie outside of conscious awareness, underpinning cognitive, social and emotional behavior throughout life. This has enormous implications: *"Well-managed babies come to expect a world that is responsive to feelings and helps to bring intense states back to a comfortable level; through the experience of having it done for them, they learn how to do it for themselves.*" (Gerhardt, 2004,

p.19) On the other hand, "*… aggression and antisocial behavior which start in childhood are the most damaging to society. They are the most consistent through life, the most linked to adult criminality and drug abuse and marital violence. "* (Gerhardt, 2004, p.188)

2.4 Parsimoniousness

The 'law of parsimoniousness' is the most basic principle in science. When different phenomena can be rationally explained by one underlying phenomenon, this should be further studied in its own right, leading to a more encompassing explanation of the overlying phenomena. In most cases, this is associated with a reductive explanation that moves from the macro-level to the micro-level. (Churchland, 2002) Throughout the history of science, parsimoniousness has led to paradigm shifts. For example:

- *Heat* as *molecular kinetic energy* explains why heat can be created through friction, and why a hot object doesn't weight anymore than a cold one does.
- *Metabolism*, *fire* and *rust* as *burning* or chemical processes requiring the presence of oxygen, unlike the activity of the sun.

In the domain of psycho-somatic medicine and more broadly – illness, wellness, addictions and so on – *subconceptual processing* is an underlying and unifying phenomenon. It is the activity of a vast and purposeful information processing network within the human brain, consisting of subconceptual nodes such as neuronal synapses. SP is conceptually compatible with the domains of artificial neural networks (connectionism), neurophysiology and cognitive neuroscience.

2.5 Two Meanings of the Concept "Meaning"

The word 'meaning' has two meanings that should not be confused. These are:

- What one can find in a dictionary – the formal definition
- What 'deeply touches' someone – poetry, art, religion, loved ones, or an important memory

The former definition by itself does not 'deeply touch' a person. It is the domain of *concepts* as mental constructs with necessary and sufficient characteristics – no emotional involvement is needed.

The latter definition encompasses what most people view is the most important part of what it means to be human – despite the fact that it is not tangible in most cases. In order to differentiate between the two definitions, this may be called the *deeper meaning*. Note that things do not by themselves have 'deeper meaning' – there is always a very complex person involved. The degree to which meaning is 'deeper' is always related to the 'depth' of the person themselves. As long as one remains at the level of *purely conceptual thinking*, there can be no 'depth' involved as a matter of principle.

A modern digital computer can be seen as a purely conceptual device. In contrast, a human being is not a type of computer, nor is the human mind a software program. The relevant difference lies in how our mind goes beyond concepts. For instance, one can conceptually analyze a poem to the minutest degree, but one does not therefore explain what is 'poetic' about it. The poetry resides at the SP level, where there are no 'necessary and sufficient characteristics', and therefore no concepts at all strictly speaking. Yet, it is here that all we hold nearest and dearest apparently originates.

In this thesis, the term ‘deep’ is used several times. ‘Deep’ is, of course, hard to define. Utterances such as “I am deeply in love.”, “This touches me deeply”, “I have a deep concern about the present issue.”, “I have deep faith in this project.”, “They have a deep belief in God.”, “She had a deep longing.” and “He was deeply motivated to achieve success.” all bear witness to this. What these examples all have in common is that ‘deep’ is – among other things – about letting go of what can be delineated in a straightforward manner. As we delve more ‘deeply’ into something, it:

- becomes more difficult to communicate conceptually
- seems to relate more to many other things
- ‘moves’ us easily, particularly as we ‘understand’ it more
- seems to become more ‘active’ in the back of our minds
- feels as if it is an integral part of us – we would be diminished or different if it no longer existed
- is more naturally described using metaphorical language

- invokes physical reactions more readily
- demands empathic 'openness' in order for us to understand and be understood
- becomes a long-lasting layer of feeling and thought that influences our life

As in the examples and characteristics above, 'deep' in most cases transcends the purely conceptual. Poetry is about 'depth', with its multiple layers of explanation and unexpected associations, use of symbolic language, and ability to 'touch' the reader profoundly without them understanding conceptually why this happens. This has huge implications – little explored – for instance, when trying to 'deeply' motivate people to stop smoking or eat less. An essential problem in this may be the transparency of the psyche – and particularly of non-conscious processes (cf. further on in this thesis).

An age-old human intuition is that 'deeper meaning' plays a very important role in sickness and in health. We see this in sayings such as 'a broken heart', 'it gets on my nerves' and so on. Recent developments in the field of psychoneuroimmunology and functional syndromes (formerly 'psycho-somatics') over the last few decades have given additional support to this intuition.

As SP deals with deeper meaning, this thesis can also be understood as a quest to develop the role of deeper meaning in health and healing.

2.6 General Importance of this Thesis

At the beginning of this 3rd millennium, people worldwide still face enormous and escalating healthcare problems that are extremely costly and appear intractable. The more resources we focus on trying to solve many of these problems – such as depression, obesity, psycho-somatic disorders and drug addiction - the worse they seem to become. Many solutions only give temporary relief, and are then followed by further deterioration.

Part of this picture becomes clearer when we look at pharmaceutical drugs. In spite of the general view that these cure diseases, for the most part they only relieve symptoms. Only a few exceptional drug categories – antibiotics and chemotherapeutics – actually offer a cure. Of course, symptom relief may be a good

thing in some cases. However, in domains such as psycho-somatics, this approach is highly problematic. Here, underlying issues often remain unmanaged and fester, while patients think that they are receiving the best care.

In this way, when we think we are drawing a solution towards us in the long term, we are often drawing it away. This is shown in the figure below: when we pull on a string wrapped around a wheel, the solution is pulled in the opposite direction.

Whether the solution is drawn towards us or away from us depends on whether it lies above or below the horizontal bar in the middle. If it lies above the bar, it is drawn towards us, whereas if it is below the bar, it is drawn away. In this picture, conceptual processing lies above the bar, while SP lies below it. This thesis deals with the importance of what lies below the bar in medicine and healthcare. We hypothesize that this view depicts a reality with huge implications for many, and indeed most areas of health and healing. We search for answers by delving deeply into the domain of SP, an area which has been studied extensively in cognitive neuroscience (see Discussion 1 of this thesis). We also translate these insights and delve deeper into them within the medical domain (see published articles and Discussion 2 of this thesis).

When someone is given a placebo for pain, fMRI shows that a number of their brain centers/regions become active – things are happening in the brain at the *objective* level. Simultaneously, they believe that the placebo will work – there is a parallel *subjective* effect. Indeed, the person *feels* less pain because they respond to the analgesic suggestion that accompanies the placebo. In a double-blind situation (placebo vs. active medication), the *treatment assumption* modulates their expectations. This is yet another example of how the mind and brain are inextricably intertwined – and in fact are one.

Interestingly, this is closely related to the effect of *empathy* between physician and patient, which can substantially relieve the *feeling* of pain. Considerable progress is now being made in our understanding of both empathy and placebo at the subjective level. However, there is still a need to ground these insights at a deeper level where the subjective and objective intersect. This is important, as it may give rise to healthcare developments that reduce costs substantially while relieving suffering in a sustainable way.

At present, there are huge gaps in our medical knowledge. Whether intentionally or unintentionally, a significant amount of effort goes into trying to conceal these gaps. On closer inspection many medical diagnoses do not identify specific diseases, but instead take some aspect of reality and put a label on it. As this approach is repeated systematically in psycho-somatics, the level of knowledge we actually have in medical science is highly overrated. The APA's DSM-IV, and to an even greater extent DSM-V, are an example of this in psychiatry. Despite many years of research, the biochemical foundations of depressive, schizophrenic, ADD and other numerous psychopathological conditions remain undetermined – see, for instance, the university textbook 'Neuroscience, Exploring the Brain' (Bear, Connors, & Paradiso, 2007). As an illustration, those who initially conceptualized ADHD warned against medicalizing it into a disease entity. However, for many medical professionals and laypersons, it is viewed as exactly that. Depression is another example: the serotonin hypothesis remains controversial at best (Kirsch, 2009), and the DSM criterion involves matching a certain number of characteristics out of a longer list – in other words it is a diagnosis that is made by convention. The issue, of course, is that if the serotonin hypothesis is not true, then what is it that underlies that which we call 'depression'? In future, this gap may be filled by SP. At present, we don't know if this is the case, and we have not researched this hypothesis, but any keen observer knows that depression is intimately related to a perceived lack of deeper meaning. The fact that mental diseases are not clearly delineated is also demonstrated by the frequency of comorbidity between them, indicating that they might be better explained as highly overlapping conditions with fuzzy borders. (Verhaeghe, 2009)

There are also gaps concealed in causal thinking. When following a causal chain, many researchers and practitioners tend to stop systematically at material points in the chain, rather than at psychological ones – although this is often not done intentionally. The end result, however, is a situation where material etiologies form the majority of medical explanations, without the psyche being taken into account.

Managing psychological aspects of a condition remains the role of care, not cure. In the best case, it is in the province of nursing, rather than residing in the hard, factual bastion of medical management. Because of this, medicine is gradually retreating into an ivory tower, with advances serving a socioeconomic purpose, rather than a scientific and patient-centered one.

Western science traditionally views diseases as entities that exist within individuals. However, for a number of health issues, an alternative and potentially better approach is to look at them from an intrinsically social perspective. In other words, a person does not 'have a disease', but instead they 'show the disease' (better termed a *health issue*) within an environment where the condition is not immediately and conceptually obvious, but instead plays itself out on a stage of overlapping subconscious patterns. One may wonder how such a setting can influence someone so that they display such symptoms. Subconceptual communication at the SP level may offer a set of explanations. In fMRI studies of empathy, for example, it has become increasingly clear how so-called *mirror neurons* or *mirror neuronal patterns* in the brain influence whether we are intrinsically social beings. (Keysers, 2011)

So, with this in mind, we can now ask ourselves what are healthcare implications of a view of the human mind/brain that does or does not incorporate the subconceptual. The latter is more clock-like, and the former is more cloud-like, as elaborated in the article *'Cloud or Clock'* that forms part of this thesis. We have posed the question from a broader perspective, addressing such issues as evidence-based medicine (EBM), placebos, empathy and causal thinking in medicine. We have also considered the implications in specific medical domains such as epilepsy, PUD, chronic pain, myocardial ischemia, and the use of methylphenidate by students to enhance study capacity. All of these research subtopics have been examined in a search for a more global answer to the question "How important is subconceptual processing in medicine?"

3 Research Question: How Important is Subconceptual Processing in Medicine?

The main research question and sub-questions addressed in this thesis are as follows:

- How important is SP in medicine?
- Is it a common ground on which seemingly diverse phenomena can be explained in a unified manner?
- May it therefore provide a new basis on which large parts of future healthcare can and should be built?
- Will it enable us to synthesize rationality and poetry (deeper meaning) into one whole, even in the domain of medicine?
- Will it allows us to truly understand the unity of the mind and body at last?
- Will it be able to drive a significant evolution (or even revolution) in medical thinking?
- Can it provide a framework that is easily communicated to and grasped by the general public, thus transcending research to become something that many people can relate to, talk about, and even be guided by its principles?
- Will it be able to solve a number of seemingly intractable healthcare problems?

- Will it lead us towards a more sustainable kind of medicine where people are respected as total beings and can take better care of themselves in a social context?
- Will empathy be valued much more highly than is presently the case?
- Will psychopharmacological substances be valued less?
- Will our efforts provide some counterweight to the current evolution towards an ever stricter biomedical approach that estranges many patients and makes them 'flee to the other side' (i.e. any CAM that is no more than an alluring tune)?

4 Publications for PhD

4.1 Listing of Publications

4.1.1 PubMed Articles

Title	Status
Cloud or Clock: Implications of the Subconscious on Placebo, Double-Blind Studies and Medicine in General	SUBMITTED
The placebo effect: how the subconscious fits in.	PUBLISHED
From Placebo to 'Open-Label Placebo' to Open Altogether	SUBMITTED
Placebo has MANY side-effects	SUBMITTED
Empathy Beyond the Conceptual Level: Core Nonspecific Factors of Psychotherapy.	PUBLISHED
From "Does it work?" to "What is 'it'?" - Implications for Voodoo, Psychotherapy, Pop-Psychology, Regular, and Alternative medicine.	PUBLISHED
Causal Thinking in Psychosomatics, with Peptic Ulcer as Case.	ACCEPTED
Serial Treatment Assumption Testing (STAT) Towards Better Evidence for Evidence Based Medicine	SUBMITTED

Title	Status
Influence of methylphenidate treatment assumptions on cognitive function in healthy young adults in a double-blind, placebo-controlled trial.	PUBLISHED
Psyche, Soma and Seizures: Mind-Body Non-Dualism Changes the Whole Picture	SUBMITTED
Helicobacter psychologicus: Psyche Meets Bacterium	SUBMITTED
The Choked Heart and How to Release it	SUBMITTED
Subconceptual Processing: Nonspecific Factor of Chronic Pain	SUBMITTED

4.1.2 Congress Entries

Title	Status
Vooraf opgenomen autosuggestie voor langdurige pijn interventie (PALPI-studie). Wetenschapsdag Domus Medica, Vrije Universiteit Brussel, Brussel 2010	PUBLISHED
Placebo as Communication to Neur(on)al Networks in Chronic Functional Pain. “Placebos in the Clinic, McGill Univ., Montreal 2012	PUBLISHED

4.1.3 PubMed Letters to Editors

Title	Status
It's Too Soon to Recommend Probiotics for Colic.	PUBLISHED
Acupuncture for Dyspnoe on Exertion in Chronic Obstructive Pulmonary Disease: no Blindness	PUBLISHED
Acupuncture for IVF: Do Not Let Needles Stand in the Way of Empathy	PUBLISHED

4.2 Short Synthetic Overview of Publications

As elaborated upon in these articles, this thesis discusses the premise that SP is important in both medicine and healthcare, and provides both a general assessment of the premise and an examination of its specific implications.

In the domain of cognitive neuroscience, SP delivers significant insight into human thinking, decision taking, motivation, and sensory and motor processing. We have elaborated upon these insights with the goal of reaching a deeper understanding of the role of empathy and placebos in health, and describe the profound implications this has for psychotherapy and CAM, as well as for double-blind studies and EBM.

With respect to double-blind studies and EBM, we have highlighted the extent of the lack of blindness in most 'double-blind' studies, and have shown how this is primarily caused by a disregard of SP phenomena. In addition, we have described a method through which double-blind studies can be enhanced: serial treatment assumption testing (STAT), which may drive significant progress in the domain of EBM in general.

For CAM and other 'healing methods', we have indicated how the insights that SP provides allow them to be studied without leaving rationality behind. The question 'does 'it' work?' is replaced by the much more relevant question 'what is the nature of the 'it' that appears to work?" In healing methods, 'it' is almost exclusively the person themselves – no other explanation is valid, no matter how strange or rational it appears. Because of this, we believe that openness in such cases is both a necessary and deeply ethical endeavor. Furthermore, it leads to better science, and ultimately to better healing. In some of the Letters to Editors, we have shown how research that does not take SP into account easily leads to erroneous conclusions – for example, with acupuncture and the use of probiotics for infantile colic.

Considering placebos, we have explained why and how openness is preferable to covert behavior, and how there is a continuum from covert placebos to complete openness – there are no strict borders. Furthermore, we have discussed how taking an open and objective view of placebos that is grounded in SP leads to a clear view of the many side effects that they have – side effects that are rarely taken into account at present.

We have also examined medical causal thinking, and have noted that disregarding the role of SP leads directly to overly simplistic reasoning. The effect of this is particularly profound in psycho-somatics, where psychological causality is often

completely dismissed, unjustifiably reducing medicine to a purely physical endeavor. We have specifically discussed the promulgation of H. pylori as the Nobel Prize ratified cause of PUD as an example of where this type of simplistic causal reasoning can lead to, although we might have taken many other examples

Turning to double-blind RCTs, we have shown that when sleep-deprived students take methylphenidate with the goal of increasing their study capacity, this actually did not have significant effects. However, in the same study, the *assumption* they made about which treatment they received (methylphenidate or a placebo) was positively correlated with their study capacity. This was not a conscious effect, but instead acted through a subconscious placebogenic pathway.

In the domain of epilepsy, we have demonstrated how the field is adversely affected by widespread 'Cartesian dualism', where the mind and brain are viewed as separate entities even though they form part of a larger whole. Both patients and physicians come to the consulting room with this mindset and, as a direct consequence, any seizure is seen as being either organic, psychogenic or of mixed nature. However, the reality is non-dualistic – the mind and brain are one. This leads to a new landscape for seizures in which psyche and soma coincide. This has significant implications for the management of seizures, and leads to a more patient-friendly approach to epilepsy.

Our examination of chronic pain has shown how research increasingly points to the role of meaning-related nonspecific factors, which take precedence over specific factors in differentiated disorders. Subconceptual Processing Theory (SPT) provides the missing link between these factors and the brain, creating a strong rationale for investigating the true origins of chronic pain – which may potentially lead to new treatments.

Cardiology is another area that we investigated, where we formulated the hypothesis that myocardial ischemia may be meaningfully influenced by the mind through SP, and specifically by precipitating coronary vasospasm. Not only may this hypothesis further our theoretical knowledge, it may also lead to practical management strategies that save lives.

Also included in this thesis are three Letters to the Editor. The relevance of these letters lies in their showing the importance of taking *non-specific factors* (more precisely the placebo effect and empathy) into account to sufficient depth in all circumstances, also and even most specifically when these circumstances lead to

publications in high profile medical journals. At the one hand this enables us to show that there are indeed more rational explanations to seemingly irrational health-related situations. At the other hand – and without falling into the trap of circular reasoning – this may further indicate the sheer strength of placebo and empathy to make an important difference, in all openness, to health and well-being of many. Pointing towards this again and again will hopefully make researchers, clinicians and patients alike more sensitive to a worldview in which rationality and human warmth match together. In the end, this is also an ethical stance. The intention is to regularly tackle another such article in PubMed and to make these critical viewpoints available to broad public.

These are just a few examples of the domains where the role of SP is critical. Through this, we hope that it is now clear that SP plays an important role in medicine and healthcare, and it should quickly become the focus of extensive research.

4.3 About Full Texts of Publications

The following are the full texts of the letters to editor, articles, and congress entries that have been written as part of this doctoral thesis. We thank the journals for their kind permission to publish these texts in this volume.

Cloud or Clock: Implications of Subconceptual Processing on Placebo, Double-Blind Studies and Medicine in General

This article explains why it is necessary to take subconceptual processing into account in order to make progress in health and health care, particularly in psycho-somatics (also known as 'functional disorders' today). This is a basic philosophical issue that arguably will be central to the future direction of medicine in general. The issue is not whether conceptual thinking needs to be abandoned completely, but whether or not it should be the exclusive area of focus as is usually the case at present.

4.4 FULL ARTICLE: Cloud or Clock: Implications of Subconceptual Processing on Placebo, Double-Blind Studies and Medicine in General

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Dirk Devroey, MD, PhD

Submitted in: “Perspectives of Biology and Medicine”

Abstract

The human mind can be viewed using two contrasting metaphors: a cloud or a clock. This distinction has important implications for our understanding of the placebo effect and double-blind studies, and, ultimately, for the way that scientific medicine as a whole needs to evolve in the 21st century. The question is whether the conceptual 'clock' model is sufficient to understand how the human mind influences health, or whether a subconceptual ‘cloud’ view is needed. The authors argue in favor of a deeper subconceptual framework.

Keywords:

Subconscious; placebo; double-blind studies; philosophy of mind

Physiology of mind

The human brain is a vast neuronal network that contains approximately 10^{11} neurons and 10^{14} synapses (Tang, Nyengaard, De Groot, & Gundersen, 2001). Each of these synapses is a processing unit that acts as a tiny analog computer. What we call the ‘mind’ is the result of the processing that takes place in this network, and in the individual neurons and synapses it contains.

This has important implications for how the ‘mind’ needs to be understood. Consider the analogy of a modern computer (Johnson-Laird, 1993) to clarify this. In a modern computer, there is only one processing thread per CPU processing core,

which executes symbolic instructions one after another (von Neumann, 1958), with each data item being held in a specific memory location. In comparison, the human brain is a highly '*parallel* and *distributed* device' (Rumelhart & McClelland, 1986). Let us examine these two characteristics further in the context of the mind:

- Parallel: many (and, in principle, all) neurons and synapses can be active at the same time (in parallel). This is analogous to 10^{14} analog computers acting simultaneously, and in fact may represent a much larger number if one considers patterns of synapses that act together as processing units. This is a vast number and represents tremendous processing power.
- Distributed: a mental 'concept' is not stored in a distinct compartment in our mind, separate from other concepts. Instead, a large number of neurons and synapses act together to allow a person to think about a concept, with the concept 'distributed' over these processing units. At the same time, concepts are physiologically intertwined, with one concept sharing many processing units with other concepts. This makes the human brain/mind extremely powerful, giving rise to capabilities such as:
    - Pattern recognition
    - Spontaneous generalization: the ability to retrieve what is common to a set of memories that match a retrieval cue (or cues) when the cue is too general to trigger a single specific memory (Rumelhart & McClelland, 1986)
    - Graceful degradation: errors in a probe are not fatal unless they make the probe point to the wrong memory (Rumelhart & McClelland, 1986)
    - Automatic content addressability: whenever any property of a memory becomes active, the memory as a whole tends to be activated, and whenever the memory is activated, all of its contents tend to become activated as well (Rumelhart & McClelland, 1986).

Some concepts are more distributed than others, and it is conceivable that relatively concrete concepts such as 'flower') are less distributed than more abstract concepts (such as 'love'). However, even simple numerical information can engage extensive neuronal networks (Nieder, 2005). Some concepts – 'broad subconceptual patterns' – may be so distributed that we do not have a clear notion of and name for them. Nevertheless, the most distributed ones (i.e. the most 'associated' ones) may well be the most stable, as may those that influence personality and wellbeing.

Of course, we are not aware of the minute details of what happens in our brain at the neuronal and synaptic level. We are aware of a concept, not of its distributed behavior and relation to other concepts. In fact, our awareness is superficial, underlain by an extremely complex mental world with many levels of increasing subtlety and complexity (Churchland, 2002). This is the 'subconscious' that guides and drives us, continually making decisions of which we normally, by definition, are not consciously aware. We can be made aware of some of these under appropriate circumstances (i.e. psychoanalysis), but not of others. Highly distributed concepts are candidates for this latter category.

Philosophy of mind

There are two philosophical views about what is important in understanding the workings of the human mind: the strictly conceptual view and the subconceptual\connectionist view. Within the strictly subconceptual view, the smallest relevant building elements are smaller than concepts but still have meaning, whereas in the strictly connectionist view, these building elements are even smaller and devoid of individual meaning (Smolensky, 1988).

According to the strictly conceptual view, mind is best understood as being composed of concepts and links between these concepts (which in themselves may be regarded as concepts). The subconceptual level can be abstracted away being of little or no importance. Thus, concepts of which we are (or can become) consciously aware are sufficient to understand the mind. The only important level below this is 'hardware', where such things as psychoactive drugs act.

In contrast, the subconceptual view asserts that the subconceptual mind is important. It cannot be dismissed without losing much of the ability to explain how the mind acts and what it is capable of doing (such as making us ill or healthy).

Vision is one field in which the existence and importance of this subconceptual level is evident (Churchland & Sejnowski, 1992; Marr, 1982; Eysenck & Kean, 1996; Zeki, 1993; Niedenthal & Kitayama, 1994). The eyes and brain receive a tremendous amount of information that is extensively processed in the subconscious before it reaches consciousness. This subconscious processing includes many decisions made on diverse levels. It is not simple and 'camera-like', but is instead very complex and

'mind-like'. What one consciously sees as a result is a highly processed world (Dennett, 1992). There are many more examples where the existence and enormous processing power of the subconscious is undeniable. These abound in the literature of cognitive neuroscience (Gazzinaga, 2009) and of the philosophy of consciousness (Dennett, 1992; Churchland ,2002).

These two competing views can be represented by two contrasting metaphors. In the conceptual view, the mind behaves as a clock (a Cartesian analogy): mechanistic, objective, and clearly comprehensible (at least to the expert). This is a positivistic view of mind, akin to Wittgenstein's hard-core positivistic view of his 'first period' (Störig, 1999), as distilled in his 'Tractatus Logico-Philosophicus' (Wittgenstein, 1998). Conversely, in the subconceptual view, the mind is a cloud: in the end unknowable, and mostly operating without conscious control. If we try to consciously grasp something on the subconceptual level, we do not seize the mind itself but a chimera that mimics it. This is reminiscent of Wittgenstein's second period, that of the 'Philosophische Untersuchungen' (Wittgenstein, 2001).

Modern medicine has developed largely on the conceptual foundation, allowing it to be regarded a 'solid' science akin to physics, and to distance itself from the realm of magic. Within present-day medicine, we see the positive results of this choice, but also the significant difficulties that arise from it. The goal must be to retain these benefits while addressing these difficulties.

Consequences for placebo

A pure placebo, in the most classical sense, is a 'drug' that contains no relevant pharmacological substance, but is administered as if there were (Shapiro & Shapiro, 1997). However, a placebo may be something other than a drug, such as psychotherapy, a medical procedure, or even the diagnosis of a medical condition (Moerman, 2002). In all cases, if a person gets 'better' by taking a placebo, it is because the placebo 'means' something to that person. It gives them the expectation (Moerman, 2002; White, Tursky, & Schwarts, 1985), hope (Plotkin, 1985; Spiro, 1998), faith (Kuby, 2001) or belief that they are being helped and are getting better. The active power does not lie in the drug, but in the person (Brody, 2000) taking the drug, as they are receiving a suggestion that placebo is (for instance) a powerful painkiller. Once the person is made fully aware that the drug

only consists of milk powder or some equally pharmacologically inactive substance, the placebo loses its power.

Pure placebos are seldom used intentionally nowadays (Shapiro & Shapiro, 1997). However, many drugs exhibit a placebo effect in addition to their pharmacological action, as shown in numerous double-blind studies (Moyad, 2002). Therefore, the placebo effect permeates medicine extensively.

What placebo researchers seldom state explicitly is that a placebo 'works' *through* the subconscious (Mommaerts & Devroey, 2012). However, this becomes obvious if one examines the phenomenon of subconceptual processing and communication (Bechtel & Abrahamsen, 2002). In the real world, the subconscious is always present and active. For instance, a man cannot make himself have an erection through *purely* conscious means without recourse to the subconscious (such as meaningful visualizations and expectations). In short, there is no erection without (auto)suggestion. Similarly, one cannot influence an erectile dysfunction through *purely* conscious means, nor, for that matter, an asthmatic condition. However, these are examples of things that can be influenced by the placebo effect, as shown in scientific studies of asthma (Butler & Steptoe, 1986), migraine (Branthwaite & Cooper, 1982) and many other medical conditions, both in regular (Shapiro & Shapiro, 1997; Moerman 2002; White, Tursky, & Schwarts, 1985; Harrington, 1997; Brody, 2000) and complementary (Peters, 2001) medicine. Apparently, a placebo 'communicates' its message to the subconscious, directing the power of the subconscious towards a specific goal. Since a placebo effect is seen with most drugs (Moerman, 2002), we can deduce that this subconscious power is very widespread. It is 'parallel' in nature, working together with everyday thoughts and many other things occurring simultaneously in the same brain, and is also 'distributed' in the sense that it activates broad subconceptual patterns, and hence has the potential to be extremely powerful.

Within the entire literature that deals with the mechanisms of the placebo effect, there is virtually no mention of the subconscious, either explicit or implicit. A Medline search for the last 30 years reveals almost no results. Nevertheless, the fact that the subconscious is intrinsic to the placebo effect has tremendous theoretical and practical implications for our understanding of health and healing, as well as for that which lies at the heart of evidence-based medicine: double-blind studies.

Consequences for double-blind studies

From the subconscious point of view, what is the exact meaning of 'blind' in the term 'double-blind'? Consciously, the patient may not 'know' whether they have taken a placebo or a pharmacologically active substance. However, they always receive much more data subconsciously than they can grasp and process consciously. Since a placebo works at the subconscious level, being consciously 'blind' is insufficient.

When a subject takes a drug, they only experience part of the drug's action at a conscious level. How much of the effect is felt consciously and how much acts subconsciously is unknown at present, but, given the complexity of the human body and mind, it is reasonable to assume that the subconscious component may be fairly large if it is proportional to the amount of processing that occurs there. For instance, consider the amount of subconscious processing required just to read this text: guiding and anticipating eye movements, chunking characters into words or even into parts of sentences, making numerous semantic associations on the fly, and so on. From a placebo perspective, the subconscious 'side-effects' (and effects) of a drug or medical procedure are at least as important as those that are felt consciously. Just asking a person whether they think that they are taking a placebo or active medication (Sharpe, Ryan, Allard, & Sensky, 2003) may provide further insight into this, but doing so cannot provide a complete picture, since this only probes conscious knowledge, not subconscious reactions.

The consequence is clear: to address the total person, 'blinding' needs to be much more than a simple passive placebo with no side-effects. By analogy, this is like putting two suitcases, one full and one empty, through an X-ray machine. While the suitcases look the same to the naked eye, the rays of the machine penetrate much deeper, creating major problems for would-be smugglers.

Ultimately, this problem is insoluble. The 'ideal' placebo is one with the same conscious and subconscious side-effects as the medication itself. This is, of course, not feasible, since it can only be achieved by using the active medication as a placebo. Therefore, double-blind studies will always be deficient, which has significant consequences, as shown in two recent examples discussed below.

Sildenafil has a significant number of side-effects, with the cumulative occurrence of *known* side-effects exceeding 100% (Dundar, Kocak, Dundar, & Erol, 2001). In addition, it is clear that a number of its 'side-effects' are not perceived consciously. These are widespread throughout the body, and the subconscious certainly senses

a number of them. In addition, sildenafil creates changes that resemble the secondary effects of sexual arousal, such as increased blood pressure and heart rate, palpitations, changes in blood flow in parts of the body, and an increase in sympathetic nerve activity in muscles (Phillips et al. 2000). This makes the 'message' to the subconscious even stronger: 'something is happening here', 'an erection is possible now'. These are powerful (auto)suggestions in an extremely suggestible domain. Therefore, to be sure of the pharmacological effect of sildenafil, it should be compared to active placebos. However, a thorough literature search conducted by the authors of the article reveals no proper studies that compared sildenafil to active placebos, let alone to ones with comparable side-effects. The conclusion is that nobody knows the nature and magnitude of the placebo effect with sildenafil.

In another example, when studies have compared antidepressants to passive placebos, approximately 75% of their effect has been shown to be due to the placebo effect, and this is now generally acknowledged. Studies that compare antidepressants to active placebos point to an even higher percentage, which may be as much as 100% (Thomson, 1982; Moncrieff, Wessely, & Hardy, 1998; Kirsch & Saperstein, 1998; Kirsch, 1998a; Kirsch, 1998b; Kirsch, 2002; Antonuccio, Burns, & Danton, 2002). Are these active placebos actually antidepressants, or is the effect due to the subconscious? For the time being, the question remains open, although from the subconceptual viewpoint the second option is more obvious.

Consequences for medicine in general

Today's scientific medicine is not yesterday's, nor is it tomorrow's. Although we do not know how medicine will evolve, it is almost certain the prevailing view of the human mind will continue to play a major role. If we disregard the subconceptual level simply to avoid 'magic', this is unjustified and in itself an unsustainable 'magical act'. So, we must ask the question again: is the conceptual or subconceptual view more appropriate for the evolution of scientific medicine?

Clearly, the conceptual approach lends itself well to experimental medicine, allowing clear-cut experiments to be performed relatively easily under controlled conditions. Is this acceptable? The answer is yes in those domains where the conceptual framework is close to reality, such as in the laboratory or emergency department.

However, the subconceptual hypothesis is more appropriate in many circumstances. Especially in the field of psychosomatics, the full reality of the human mind needs to be taken into account, as this is needed to make people better. To constrain experimentation to what can be investigated on a conceptual level is to disregard the subconceptual dimension, which is an irrational stance. We are certainly not entitled to do this, especially in light of the placebo effect. Another issue that highlights this is the continued failure of medical knowledge extraction for use within expert systems, which is largely due to the generally acknowledged fact that medical knowledge can only be partially formalized i.e. 'conceptualized' (Van Der Lei, 1994). Another area is that of medical empathy, which is "needed even when it is quite obvious what emotion label applies to a patient" (Halpern, 2003), thus transcending the purely conceptual ((Mommaerts, Goubert, & Devroey, 2012)).

On the other hand, we must not content ourselves with saying that it doesn't matter whether a patient gets better due to a drug or to the placebo effect. If we do that, we revert to primitive 'magical thinking', pretending to yield a power that we do not possess, one that actually resides within our patients (Frank, 1973). At that moment, science stops.

Conclusion

The subconscious and its role in the subconceptual view of mental processes have major implications for medicine in general. Double-blind studies with passive placebos, currently at the cutting edge of scientific medicine, only give a crude picture of the relative roles of the placebo effect and pharmacology with a medication. In many cases, the placebo effect may be much more significant than currently depicted.

We should be extremely cautious not to slide back to indiscriminate magical thinking. Medicine has become 'scientific' in order to rid itself of 'magic'. However, some detrimental 'magical' elements may have crept into the way we perform science itself. Simply disregarding any part of reality, including that of the subconscious, cannot be called truly scientific. On the contrary, this opens the door to many types of alternative medicines that are, from the scientific standpoint, clearly wrong. It is easy to blame those that turn to alternative medicines for their unscientific gullibility, but what they are actually doing is to search for real solutions to real problems that, in many cases, have no solution within a strictly conceptual

framework. It is incumbent upon us to provide these people with the solutions they need, while remaining rational and scientific.

Bibliography

Antonuccio, D.O., Burns, D.D., & Danton, W.G. (2002). Antidepressants: A Triumph of Marketing Over Science? Prevention & Treatment, 5, Article 25.

Bechtel, W., & Abrahamsen, A. (2002). Connectionism and the mind. Oxford: Blackwell.

Branthwaite, A., & Cooper, P. (1981). Analgesic Effects of Branding in Treatment of Headaches. British Medical Journal (Clinical Research Ed.), 282, 1576-1578.

Brody, H. (2000). The placebo response. New York: HarperCollins.

Butler, C., & Steptoe, A. (1986). Placebo responses: an experimental study of psychophysiological processes in asthmatic volunteers. British Journal of Clinical Psychology, 25, 173–183.

Churchland, P.S. (2002). Brain-Wise - Studies in Neurophilosophy. Massachusetts: MIT Press.

Churchland, P.S., & Sejnowski, T.J. (1992). The computational brain. Massachusetts: MIT Press.

Dennett, D.C., (1992). Consciousness Explained. London: Penguin Press

Dundar, M., Kocak, I., Dundar, S.O., & Erol, H. (2001). Evaluation of side-effects of sildenafil in a group of young healthy volunteers. International Urology and Nephrology, 32(4), 705–708.

Eysenck, M.W., & Keane, M.T. (1996). Cognitive psychology. Hove: Psychology Press.

Frank, J.D. (1973). Persuasion and Healing. Baltimore: Johns Hopkins University Press.

Gazzinaga M.S (2009). The Cognitive Neurosciences: Massachusetts: MIT Press.

Halpern, J. (2003). What is clinical empathy? Journal of General Internal Medicine, 18(8), 670–674.

Harrington, A. (1997). The placebo effect - an interdisciplinary exploration. Cambridge, MA: Harvard University Press.

Johnson-Laird, P. (1993). The computer and the mind. London: Fontana Press.

Kirsch, I. (1998a). Reducing noise and hearing placebo more clearly. Prevention & Treatment, 1, article 0007r

Kirsch, I. (1998b). On the importance of reading carefully: a response to Klein. Prevention & Treatment, 1, article 0009r.

Kirsch, I. (2002). The emperor's new drugs: an analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prevention & Treatment, 5, article 23.

Kirsch, I., & Sapirstein, G. (1998). Listening to prozac but hearing placebo: A meta-analysis of antidepressant medication. Prevention & Treatment, 1, article 0002a.

Kuby, L. (2001). Faith and the placebo effect. Novato: Origin Press.

Marr, D. (1982). Vision. New York: W.H.Freeman & Company

Moerman, D. (2002). Meaning, medicine and the 'placebo effect'. Cambridge: Cambridge University Press.

Mommaerts, J.L., & Devroey, D. (2012). The placebo effect: how the subconscious fits in. Perspectives in Biology & Medicine, 55(1), 43-58.

Mommaerts, J.L., Goubert, L,, & Devroey, D. (2012). Empathy beyond the conceptual level: core nonspecific factors of psychotherapy. Perspectives in Biology & Medicine, 55(2), 175-182.

Moncrieff, J., Wessely, S., Hardy, R. (1998). Meta-analysis of trials comparing antidepressants with active placebos. British Journal of Psychiatry, 172, 227–231.

Moyad, M.A. (2002). The placebo effect and randomized trials: analysis of conventional medicine. Urologic Clinics of North America, 29, 125-133.

Niedenthal, P., & Kitayama, S. (1994). The 'hearts' eye. San Diego: Academic Press.

Nieder, A. (2005) Counting on neurons: the neurobiology of numerical competence. Nature Reviews Neuroscience, 6(3), 177-90.

Peters, D. (2001) Understanding the placebo effect in complementary medicine. Edinburgh: Churchill Livingstone.

Phillips, B.G., Kato, M., Pesek, C.A., Winnicki, M., Narkiewicz, K., Davison, D., & Somers. V,K, (2000). Sympathetic activation by sildenafil. Circulation, 102, 3068–3073.

Plotkin, W.B. (1985). A psychological approach to placebo: the role of faith in therapy and treatment. In: L. White, B. Tursky, & G.E. Schwarts (Eds.), Placebo: theory, research and mechanisms. New York: Guilford Press.

Rumelhart, D.E., & McClelland, J.L. (1986). Parallel distributed processing. Massachusetts: MIT Press.

Shapiro, A.K., & Shapiro, E. (1997). The powerful placebo. Baltimore: The Johns Hopkins University Press.

Sharpe, L., Ryan, B., Allard, S., & Sensky, T. (2003) Testing for the integrity of blinding in clinical trials: how valid are forced choice paradigms? Journal of Psychotherapy and Psychosomatics, 72(3), 128-131.

Smolensky, P. (1988). On the proper treatment of connectionism. Behavioral and Brain Sciences, 11, 1–74.

Spiro, H. (1998). The power of hope – a doctor's perspective. New Haven/London: Yale University Press.

Störig, H.J. (1999). Kleine weltgeschichte der wissenschaft. Frankfurt: Fischer Taschenbuch Vlg.

Tang, Y., Nyengaard, J.R., De Groot, D.M., & Gundersen, H.J. (2001) Total regional and global number of synapses in the human brain neocortex. Synapse 41(3), 258-273.

Thomson, R. (1982). Side-effects and placebo amplification. British Journal of Psychiatry, 140, 64–68.

Van Der Lei, J. (1994) Computer-based decision support. In: P. Barahona, & J.P. Christensen (Eds.), Knowledge and decisions in health telematics. Amsterdam: IOS Press.

von Neumann, J. (1958). The computer and the brain. New Haven/London: Yale University Press.

White, L., Tursky, B., & Schwarts G.E. (1985). Placebo: theory, research and mechanisms. New York: Guilford Press.

Wittgenstein, L. (1998) Philosophical investigations/philosophische untersuchungen. (4th ed.). Oxford: Blackwell.

Wittgenstein, L. (2001). Tractatus logico philosophicus. London: Routledge.

Zeki, S. (1993). A vision of the brain. Oxford: Blackwell.

The Placebo Effect - How the Subconscious Fits in

This article describes how every explanation for the placebo effect can be reduced to autosuggestion. Since the placebo effect has been shown to be relevant in the majority of medical domains, a proper understanding of this is needed that takes into account all aspects of the human condition. This will also reveal new avenues towards theoretical and practical advances across a wide range of health issues.

4.5 FULL ARTICLE: The Placebo Effect - How the Subconscious Fits in

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ABSTRACT The placebo effect is very well known, being replicated in many scientific studies. At the same time, its exact mechanisms still remain unknown. Quite a few hypothetical explanations for the placebo effect have been suggested, including faith, belief, hope, classical conditioning, conscious/subconscious expectation, endorphins, and the meaning response. This article argues that all these explanations may boil down to autosuggestion, in the sense of "communication with the subconscious." An important implication of this is that the placebo *effect* can in principle be used effectively without the placebo itself, through a direct use of autosuggestion. The benefits of such a strategy are clear: fewer side effects from medications, huge cost savings, no deception of patients, relief of burden on the physician's time, and healing in domains where medication or other therapies are problematic.

PLACEBO AND THE PLACEBO EFFECT

A much-cited definition of *placebo* is from Shapiro and Shapiro (1997): "any therapy (or that component of any therapy) that is intentionally or knowingly used for its nonspecific, psychological, or psychophysiological, therapeutic effect, or that is used for a presumed specific therapeutic effect on a patient, symptom, or illness but is without specific activity for the condition being treated" (p. 41**).** What *nonspecific* means and how it relates to the psyche has been written about extensively yet inconclusively. In the end, the term *nonspecific* doesn't say anything about the crux of the matter.

Talking about placebo, one first has to distinguish between "placebo effect proper" and "perceived placebo effect." The latter is the effect of one or more of the following: regression to the mean, natural history of disease, investigator effects (such as the nocebo effect called "white coat hypertension"), and Hawthorne effect–

like changes in patients' behavior (patients becoming sensitized to the problem under investigation, once they are included in a trial). In this article, *placebo effect* denotes the "placebo effect proper," and *placebo* anything that provokes this. This said, the placebo effect may be seen as the primary and non-discernible effect on a person brought about by using a placebo, which is in itself inert regarding this very effect or part of it. It is what happens in time between the contact with the placebo and the physiological/psychological consequences of the placebo effect. There is no clear dividing line between the effect and the consequences. However, using the term *placebo effect* puts emphasis on *how* an external event (such as the taking of a drug) gets translated into a discernible internal event (such as feeling better or the lowering of blood pressure). In this, the external event is not the final cause but a precipitating factor inducing something within the person that itself leads to the consequences of the placebo effect.

The word *placebo* usually makes one think of drugs. But placebos can also be objects (syringes, a copper bracelet), rituals (physical examination, anamnesis), places (doctor's office), relationships (with doctors, self-help groups), thoughts (about performances of medicine), and other entities such as touch, words, social interventions, a tattoo, or a surgery scar. In fact, anything that has meaning to someone can act as a placebo. Thus, with each encounter with the medical system, a patient's placebo response is being shaped (Peck and Coleman 1991). Even the act of diagnosing a person with a medical condition can have a placebo effect (Moerman 2002). From the other side, in view of the complexity of the human body-mind system, probably almost any health problem can be influenced through the placebo effect. Many authors agree that the average placebo effect of *all* present-day medications together may be higher than half of the total action, still comparing very favorably to pre-1900 medications with placebo effects of mostly the full range (Shapiro and Shapiro 1997).

MECHANISMS OF THE PLACEBO EFFECT

Many mechanisms have been described to explain the placebo effect. In this article, the five mechanisms most prominent in the medical literature are looked at in-depth. However, there are also other hypothetical mechanisms, including: optimism/re-moralization, conviction, relationship with the prescriber, magic, diversion of attention, symbolic power, oneness of body and mind, transference, relief of guilt, sense of control, diminishment of anxiety, fitting in the story, (self-)hypnosis, emotional appeal, and response-appropriate sensation theory (Benson

and Epstein 1975; Brody 2000; Byerly 1976; Evans 1981, 1985; Fisher and Dlin 1956; Frank 1973; Glaser and Kiecolt-Glaser 1994; Hahn 1985; Houston 1938; Johnson 1994; Markus 1983; Miller, Colloca, and Kaptchuk 2009; Moerman 2002; Peck and Coleman 1991; Sarno 1998; Spiro 1998; Wall 1993). These mechanisms overlap to a huge degree, which in itself already points to a probably parsimonious explanation. Indeed, they can all be described as *autosuggestion*, in the sense of "communication to the subconscious." When looked upon from a neurophysiological and neurophilosophical perspective, not hope/faith as such, but *true* hope/faith has an effect when reaching the subconscious and becoming autosuggestion (Churchland 2002; Mommaerts 2000). One cannot purely consciously decide to have true hope, faith, or expectation, just as one cannot consciously and effectively wish oneself into getting better through a placebo pill or procedure. In this hypothetical case, the placebo pill would even be senseless. Instead, placebo works through the subconscious being appealed to—be it, in the case of placebo, in a covert way. In general, however, the subconscious is painstakingly avoided in medical literature, explicitly as well as implicitly.

Faith/Belief/Hope

Generally, people take medication because they think it makes them better. At least, that is their hope. According to many authors, such as W. B. Plotkin (1985) and H. Spiro (1998), hope or faith constitutes much of the basis for the placebo response. The placebo itself is the symbol or carrier of hope, which overlaps very much with faith and belief. Technology, medical authority, and even sympathy are seen as eliciting the placebo response only indirectly, by virtue of the effect they have on the patient's beliefs. It is the *belief* in the treatment, therefore—something that lies inside the patient's mind—that sets off the placebo response (Evans 2003). Faith/belief/hope has in fact frequently been related to regular medicine in the past. According to Sir William Osler in 1932, it was seen as "the great stock in trade of the profession . . . the foundation of therapeutics" (Shapiro and Shapiro 1997, p. 58).

Faith is not to be seen in the purely conceptual sense that "I have faith that the sun will shine tomorrow." What is meant is a deep feeling of faith, such as is the case when someone really believes in God. Only "deep faith" can bring about healing. Its meaning, its message, has to be a personal conviction, an inner

certainty—what exactly you consciously believe is unimportant for this matter. By contrast, having superficial "small faith" can even bring about a negative investment, with as end result the opposite of what deep faith would have brought. If research does not take this difference into account, then of course the effect of faith may turn out to be nil.

Putting forward *hope* as a placebo mechanism may shed some light upon why the placebo effect plays a bigger role in clinical pain than in experimental pain (Beecher 1955). In the latter case, hope is not so readily relevant except when the pain lasts long or is intense. This explains the observation that placebo analgesic effects are larger for those forms of experimental pain that are more stressful or of longer duration (Jospe 1978). Where hope to be relieved from pain is stronger, the placebo effect is more active.

The side effects of pure placebos in double-blind studies are often similar to those of the drugs to which the placebos are being compared (Ross and Olson 1981). It is not clear how these side effects in themselves can be engendered by hope. *Expectation* may be a better model. Subjects who expect side effects get what they expect. At the utmost, one could say that the subject "hopes" to have the side effects, as these are seen as proof of receiving the active medication.

In conclusion, faith/hope/belief cures (or heals) when it is deep, true, touching one's inner self. It achieves the placebo effect when it constitutes a kind of "communication to the inner self"—that is, when it acts as one kind of autosuggestion.

Classical Conditioning

Classical conditioning is the pairing of an unconditioned stimulus (UCS) with a conditioned stimulus (CS) until the CS elicits the same response as the UCS. The term is mostly used with the implicit assumption that the subject is not consciously aware of the CS-UCS association, or at least that the subject's conscious awareness is not directly involved. The CS can be very concise (such as a particular medication) or very broad (such as the healing environment, including the smell when entering a hospital, the doctor's and nurse's attitude towards the patient and others, ideas of "science" and "caring," the erroneous idea of having the right to be perfectly healthy or get the perfect treatment, and so on).

Probably the first to investigate a conditioned placebo effect from drugs was Pavlov (1927). He reported that effects from morphine injections occurred in

conditioned animals already when he was preparing the injections or when he placed the dogs in the experimental chamber where they had previously received morphine. The dogs reacted in these cases upon their expectation of being reinjected with morphine. A good example of human conditioning towards placebo effect is seen in a study by Smith and McDaniel (1983). In this study, placebo conditioning clearly reduced the immune response to tuberculin, thereby showing also once again placebo's substantial power.

The classical conditioning model traditionally bypasses any reference to the subconscious being more complex than just a set of simple reflexes. Complex meaning is, however, always important in situations of classical conditioning. Indeed it is only the deeply meaningful perception of environment and conditions that acts upon one. Even Pavlov's dogs expected the food when the bell tolled, in a way that indicated the bell and the food meant something to the dogs. The same can be seen in human cases. For instance, in an experiment in which asthmatics were given a placebo broncho-constrictive inhalation and a placebo drug, pulmonary function reacted in both cases in a placebo-prone manner. The most important predictive factor in this setting was the manner in which individuals perceived the experimental setting as consequence of the suggestions they received together with the placebo (Butler and Steptoe 1986).

Taking the argument even further, both unconditioned and conditioned stimuli in the classical conditioning paradigm are themselves in fact meanings. To Pavlov's dogs, *food* means "yummy yummy," thus saliva flows. Then by association the bell comes to mean "food will come," thus "yummy yummy" and saliva flows. Neither food nor bell make saliva flow by themselves: "yummy yummy" does. This is therefore the real stimulus or UCS, while "bell–yummy yummy" is the real CS. If the dog becomes brain-damaged in a specific way, the bell doesn't mean anything anymore, and there's no flow of saliva.

A suggestive message can come from prior exposure and association. Renewed exposure then carries the suggestion of probably leading to the same result. Looked upon in a mechanical way, this fits the conditioning paradigm. However, it doesn't work without the deeper layer, which is why many authors such as Reiss (1980) put expectation before conditioning. Expectancies can also be formed without direct personal experience, for example, through observational learning, verbal information, persuasion, and other symbolic processes (Peck and Coleman 1991). Price and Fields (1997) contend that although classical conditioning

can change one's expectation, other types of learning can also contribute. For example, expectation can reflect knowledge about the therapeutic agent, the circumstances under which it is administered, and the condition to be treated. Expectation of relief may cause a placebo response without prior exposure to a therapeutic agent, though such exposure certainly will increase expectation.

Some authors appear to see conditioning as a kind of "subconscious expectation," where the subconscious is seen as a black box. In a specific experiment in which the subjects weren't told the real aim of the experiment, Amanzio and Benedetti (1999) noted that placebo responses occurred "without expectation" of pain relief. If subjects were previously conditioned with either morphine or ketorolac, the lack of expectation cues only reduced but did not prevent the placebo effect. Thus, previously conditioned subjects experienced analgesic effects even "when not expecting any." However, the fact is that such subjects do expect an analgesic effect, not consciously but subconsciously—and apparently, that's enough. The distinction generally made between conditioning and expectation results from not taking the subconscious into account in the concept of expectation. In short, conditioning seems to be only one of the mechanisms by which the expectancies exert their effect (Peck and Coleman 1991). This means explanations for the placebo effect may be offered at different process levels but still prove to be fully compatible to each other.

On the other side, there is a continuum between conditioning and what is no more than physiological reflexes. R. J. Herrnstein (1962) reported that the effects of scopolamine injections in rats also appeared after saline injections in "conditioned rats." Several authors see in this an example of animal conditioning. However, no internal mental processing is necessary in this case. Generally put, if there is no "meaning," the process should not properly be called "conditioning." In the case of the "conditioned" rats, what was observed may be a purely physiological reflex and change, such as that due to volume distention of the cardiovascular system, without any expectation involved. To call this a placebo effect is confusing: no conclusions about classical conditioning should be drawn from mere physiological changes.

Conscious/Subconscious Expectation

Many authors suggest that *expectation* is a salient determinant of the placebo effect in general and placebo analgesia in particular (Laska and Sunshine 1973; White, Tursky and Schwarts 1985). However, there is little or no explicit

mention of *subconscious* expectation. An exception is the single case stating that "questions about the possibility of unconscious expectancy remain unresolved" (Hoffman, Harrington, and Fields 2005, p. 257). Moreover, there is only rarely even an implicit reference to the subconscious. Most authors use the word *expectation* as if only conscious expectation is meant—this is, what one can consciously put into words and communicate in a formal way. To assess conscious expectation, one can simply ask the subjects of an experiment about their expectations before the experiment begins, as where placebo reactors are (thought to be) identified before the trial by asking the subjects what they expect as outcome of the therapy (Wall 1993).

Most authors agree that expectation can be very powerful. It can even override pharmacological effects, so that expectancies contrary to the pharmacological effect of a drug can in some cases prevail over the drug's effect itself (Kirsch 1985). Moreover, expectations (and thus the placebogenic effect) are nowhere so high as with surgery. This should be no surprise, since the meaningful aura around surgery is quite impressive: surroundings, surgeon's personality, anesthetic, incision, experiences of friends and other patients, length of the illness, amount of pain, accounts of surgery in the media (Johnson 1994). As is to be expected, expectations as well as the placebo effect heighten through confidence in the obtainment of relief. This is clear, for instance, in specific research about branding, in which branded placebos are more effective than unbranded placebos in relieving headaches; branded active ingredients are more effective than unbranded active ingredients; and a familiar brand is more effective than an unfamiliar brand. Moreover, the placebo effect of the branded placebo can even be higher than the pharmacological effect under study (Branthwaite and Cooper 1981). In an experiment by Amanzio et al. (2001), analgesics given surreptitiously had fewer effects than the same analgesics given openly. This shows the effect of expectation without the use of a placebo arm in the study. The underlying mechanism is the same as in a placebo-controlled trial. Here too, "no expectation" means "no placebo effect."

In former times, prior to rigorous studies, a new drug was often greeted with much enthusiasm and therapeutic effectiveness in the vast majority of patients (70–90%), due in large part to a strong placebo effect evoked by the expectations of investigators and clinicians. After better controlled studies, the enthusiasm typically dipped to a low level, and so did the therapeutic effectiveness on the field. This has

been described as a recurrent pattern (Benson and McCallie 1979). A well-known adage from the 19th-century French physician Armand Trousseau notes that: “You should treat as many patients as possible with the new drugs while they still have the power to heal.”

One’s expectation of relief can be modified without prior exposure/conditioning to the treatment under question. It has therefore been recommended to deliberately change expectations prior to performing the procedure, through information, persuasion, or learning from others who have been helped by such procedures (Peck and Coleman 1991). If you give someone the expectation of cure, for example, by showing others who apparently get better, then in the same kind of environment this can lead to a positive placebo effect, even without the need of any positive pharmacological action. This probably accounts for many of the successful outcomes of 19th-century and earlier medicine. (By contrast, practitioners who use weak non-placebos, or who primarily rely upon placebos, will weaken the non-placebo component of their therapy.) In principle, one can rely purely on placebos and still strengthen the placebo effect of one’s actions, even if the medication fails, because it is a well-documented characteristic of human nature that failure leads more readily to “more of the same” than to a reconsideration of the working hypothesis (Baron 1990). If the medication fails, the general deduction in practice quite often is that one didn’t use enough of it. This helps explain why, although 18th- and 19th-century bloodletting almost always failed, it only drove most physicians to more bloodletting, up to utter extremes and including the death of the first president of the United States (Shapiro and Shapiro 1997).

The special nature of an intervention may increase expectation. Thus, the flavor of exoticism that surrounds therapies such as acupuncture, the high-tech magic of treatments like ultrasound or laser therapy, or the unusual nature of a therapeutic encounter, such as history taking in homoeopathy, may all increase the placebo effect (Ernst 2001). Expectations of clinicians themselves can also be effective in heightening placebo effects even without (consciously) involving patients. In an experiment by Gracely et al. (1985), the effect of a pure placebo painkiller in the context of soothing the pain of the extraction of wisdom teeth was substantially heightened simply by telling the clinicians (dentists) that it might contain an active product versus telling them that it was only a placebo. The patients’ expectations were heightened by the clinicians’ expectations, without consciously conveying anything. It all happened on a subconscious level.

Conceptually very close to expectation is *anticipation*. The latter seems just a degree stronger or less doubtful. When studying postoperative patients responding to analgesic drugs and to placebos, Lasagna et al. (1954) observed that a positive placebo response indicated a psychological set predisposing to anticipation of pain relief, including in the case of morphine and other pharmacologically active drugs.

Expectation is mostly seen as a kind of "conscious belief." However, it is clear that conscious expectation alone cannot have a placebogenic effect. Expectation does not operate on a conscious level. You "know" that you expect something like you "know" that your heart beats. But you cannot consciously start or end, nor even heighten or lower, your expectation as a matter of simply deciding to do so. Likewise, you cannot consciously heighten or lower the frequency of your heart beat without taking recourse to subconscious help such as by visualization. Moreover, the depth of your belief/expectation—whether it deeply touches you, whether it moves your "heart" or "soul"—is also a factor. If you consciously have an expectation but at the same time you do not have that expectation deep inside, then it will hardly have any effect. D. Evans (2003) sees "belief" as underlying both the conditioning theory of placebo and the expectancy-based theory. Expectancies are simply beliefs about the future, and conditioning can be seen as one way in which such beliefs are acquired. The evidence of direct experience may be compatible or at variance with other sources of belief, such as the voice of authority.

Interestingly, expectation also plays a big role in psychotherapy. Most clinical psychologists are eclectic, rather than belonging to a particular school of psychotherapy. This has led to an emphasis on ingredients common to all therapeutic schools, the most central of which is the patient's expectation of benefit. This is frequently assumed to be ultimately responsible for the effectiveness of placebos (Bootzin 1985). In this vein, A. K. Shapiro and L. A. Morris (1978) tend to equate psychotherapy with the placebo effect. They note that while the placebo effect is commonly believed to be just a superstitious response to a sugar pill, it is actually an important ingredient and perhaps the entire basis for the popularity and effectiveness of most, if not all, methods of psychotherapy.

Endorphins

It has been well documented for quite a while that endorphins are an important element in how the body-mind complex deals with pain in a placebo setting, although sometimes with mixed support (Grevert and Goldstein 1985;

Levine et al. 1979; Peck and Coleman 1991). Some authors see the modulation of endorphins in a placebo setting as an “explanation” or “mechanism” of the placebo effect (Levine, Gordon, and Fields 1978). But what then causes the change in endorphins? In fact, this change is itself the consequence of the placebo effect: it is proof that such consequences can be material, but it is not an explanation. Wall (1993) clarifies this with a nice analogy:

> If a newspaper headline reads: “Scientists discover the origin of music and poetry” followed by an article showing that music could not be performed when curare prevented the effect of acetyl choline released from the motor axons [and the performer was, thereby, paralyzed], one would not be overwhelmed by the insight into the nature of music and poetry. Similarly, it is not clear what insight into the overall placebo phenomenon is provided by showing that some link in the machinery involves endorphins. (p. 97)

From another viewpoint, one can say that the change in endorphins is part of the placebo effect, with body and mind acting as one: there is no cause and effect involved, since there is no time lapse in between, any “movement of mind” being at the same time a “movement of body.” However, from this viewpoint, endorphins still do not explain the placebo effect. They only make it more complex, as the whereabouts of our endorphins become part and parcel of our subconscious mental processing.

The same is true for the changes seen in the domain of neurohormones and of the immune system, as well as for regional metabolic brain changes. Changes in many brain regions are clearly associated with the placebo response, with increases in some domains, decreases in others (Mayberg et al. 2002). These changes are broadly the same as those seen with active medication, which may indicate a common pathway. In the domain of pain, lots of research points to the same conclusion: placebo conditions can show large reductions in pain and in brain activation within pain-related regions (Price et al. 2007). In any case, although such bodily changes are sometimes used in order to explain the placebo itself, they actually do not explain but merely point to the huge complexity of mind-body unity.

Meaning Response

Meaning can be something that one looks up in a dictionary, but this is not what is meant here. Something gets a “deeper meaning” when it touches you

deeply, and in the case of emotions it may prone to change your physiology (as in blushing or changes in blood pressure).

The *meaning response* is the set of physiological and psychological effects of meaning in the treatment of illness. It follows from the interaction with the context in which healing occurs, such as the power of the laser in surgery, or the red color of a stimulating medication (Moerman 2002). The placebogenic influence of colors of medication, for instance, can be explained by their "meanings": *red* typically means "up," "hot," or "danger," while *blue* means "down," "cool," or "quiet" (Moerman and Jonas 2002). Meaning is also involved with the placebogenic effect of surgery, the shedding of blood being inevitably meaningful. In addition to this, surgical procedures usually have compelling rational explanations, which drug treatments often do not have (Moerman and Jonas 2002).

Jerome Frank saw this notion of *meaning* as what lies behind all psychotherapies. He noted that human beings do not react to facts or events themselves, but to their meanings. Psychotherapy can thus be seen as the transformation from negative to positive of meanings that patients attribute to events (Holland and Guerra 1998).

A placebo provokes a meaning response, like a key in a slot. Before the placebo turns up, meaning in the sense of the ability to respond to something meaningful is of course already subconsciously present, and so is the power of this meaning. The placebo only serves to awaken what is already there. It is like a push given in the direction of a person's faculties of self-healing. The "deeper" the meaning response goes, the better it reaches the subconscious, thus the more it is a genuine kind of autosuggestion.

WHERE THE SUBCONSCIOUS FITS IN: THE CONCEPT OF AUTOSUGGESTION

A lot of mental processing happens beyond the level of conscious processing. A good example of this is vision (Churchland and Sejnowski 1992; Marr 1982). Conscious vision is only a distinct end-product of a tremendous amount of processing on a subliminal level. Moreover, this subconscious level is already full of "meaning": a lot of decisions have been made before we actually consciously "see" something (Dennett 1992). In the human mind/brain, this mechanism is all-pervasive (Zeki 1993). A meaningful lot happens on a subconscious level, and taking this into account may well be very important for health and well-being.

Autosuggestion is where the subconscious fits in. Although Freud

understood autosuggestion as straightforward suggestions of "getting better/having fewer symptoms every day" (Grünbaum 1984), in this article autosuggestion is about "deep meaning"—this is, how one becomes deeply touched by something. Imagine your dearest pet dies and you are deeply touched. Tears come up, sadness, mourning. Your body reacts to your grief in different ways. How does this come about? How does one become "deeply touched"? This death awakens something inside you. It is like a very complex key. Autosuggestion is the enactment of such keys, which can provoke feelings or other alterations in body and mind.

One cannot consciously decide to have less pain. The effect of consciously wanting it is nil. It has to reach one's subconscious, or deeper mind, where it can be transformed into action. The pattern "I expect this medication to relieve my pain" means that taking this medication "communicates" to "me" that my pain will be relieved. The placebo effect is proof that our deeper minds are capable of many very complex things and of a kind of purpose.

Placebo as Autosuggestion

Autosuggestion in this sense brings together the placebo effect that we see in almost all regular and alternative medicine's medications and actions, psychotherapy, "miracle cures," and hypnosis. It is a concept and domain that one can communicate about, investigate, ameliorate, and make practically available.

Table 1 presents some patterns of mental processing in the form of phrases. The phrases are examples of how it is possible to put "explanations" of placebo in the form of overlying patterns of autosuggestion. The patterns are not actually present in the subconscious as these concrete phrases, but the patterns can be seen as conglomerates of meaning.

Table 1

"EXPLANATIONS" OF PLACEBO IN THE FORM OF OVERLYING PATTERNS OF AUTOSUGGESTION.

Hope/Faith
"I believe that this will cure me. It will definitely cure me."
"I hope so, I long to see it become true. That's what I want."

"At other occasions, drugs have helped me. So I believe they will help me now."

Expectation

"It will become true. I will get better again."

"This device will make me feel better, as it did before."

"This new drug is the latest development in medical science. It will surely be better than anything else."

Meaning response

"This means a lot to me. There just has to be something in it that is able to relieve my suffering. I am sure it will."

PLACEBO-PRONENESS VERSUS SUGGESTIBILITY

The placebo effect generally shows poor correlation with standardized tests of (hypnotic) suggestibility, there being little correlation between tests of suggestibility in a laboratory situation and the placebo effect in a clinical setting (Shapiro and Shapiro 1997). However, suggestibility tests are standardized tests, whereas suggestibility itself (and the placebo effect) is influenced by so many objective and subjective factors (context-sensitive) that it can hardly be standardized. Another critique is that these tests are mainly hypnosis-oriented, and they painfully lack sufficiently standardized guidelines for administration and interpretation (Shumaker 1991). It should therefore come as no surprise that different tests show little correlation with each other. They are no good measure for real-life suggestibility (Barber, Spanos, and Chaves 1974).

After a long search, it has been concluded that no personality of "placebo-responder" exists, and that virtually anyone can respond significantly to placebos given the right circumstances (Peck and Coleman 1991). A person who has little placebo response to a tablet may react much more so to a saline injection. Furthermore, placebo response may be culturally colored. In general, injections engender higher expectations in the United States than in Europe and have higher effectiveness, such as for relief of migraine (de Craen et al. 2000). Logically, then,

there should be no fixed percentage of placebo effect. In fact, depending on characteristics of the clinical situation, described placebo effects can vary from 0 to 100% (Richardson 1994).

The same is true for suggestion in general. No characteristics of "suggestible persons" have yet really stood the test of time. Suggestibility depends mainly on the person-context fit. Even the physiological change brought about by (auto)suggestion/placebo varies when the subjective result is the same, as in the case of placebo analgesia. The expectation of pain relief normally acts via endorphin pathways, but this can be changed into other pathways by prior experience (or "conditioning") with an NSAID painkiller (Amanzio and Benedetti 1999; Benedetti, Arduino and Amanzio 1999). With such a diversity and context-proneness, it comes as no surprise that there is no consistent relationship between placebo response and suggestibility tests (Evans 1981).

IS PLACEBO JUSTIFIED DECEPTION?

This section is definitely not about empathy (caring for the patient, providing genuine encouragement, respecting uniqueness), which can also heighten hope, expectations, or meaningfulness (Barrett et al. 2006), but *not* through deception. Instead, this section is about "placebo proper." Cabot (1978) observed that "It never occurred to me until I had given a great many 'placebos' that, if they are to be really effective, they must deceive the patient. . . . It is only when through the placebo one deceives the patient that any effect is produced. It is only when we act like quacks that our placebos work" (p. 189).

Many doctors dislike the idea of placebo and like to discuss it even less. However, it is important to engage with this practice that is still very much among us, because some real dangers stem from the deceptiveness of placebos. First, the use of placebos can create a loss of confidence (in doctors, colleagues, medicine) if patients find out. Second, active placebos (pharmacological agents used mainly or solely for their placebogenic purposes) bring huge costs and many side effects. Third, the use of placebos heightens an inappropriate dependence on medicine in general, thereby lowering the power to self-heal. Additionally, the use of pure placebos engenders litigation suits for malpractice unless the physician has been forthright beforehand. The notion of "informed consent" thus actually precludes placebo: strictly speaking, prescribing a placebo is impossible without breaking the law. Furthermore, placebos do not bring real cures, they only alleviate symptoms. With this in mind, it is very thought-provoking that present-day evidence-based

medication, with a few exceptions such as antibiotics and chemotherapeutics, acts purely symptomatically. Finally, in any case, to really go deeper, deception will never do. It may well be that “only truth can truly cure.” The placebo effect unrightfully mystifies faith healing and many alternative medicines with probably no further basis than this, and it impedes the further development of medical science itself, thereby directly hampering tremendous cost savings and at the same time a better, deeper and more encompassing health for all.

Despite these dangers, different authors make the case that we should consciously take as much advantage as possible of the placebo effect because it is so powerful. Placebo may be a deception, but what if deception brings health or even saves your life? Moreover, dropping the use of the placebo effect from regular medicine (if it could be done) would give to other, less well-meaning parties the exclusive advantage of using it as they have always done. That is not something to look forward to. Indeed, one of the reasons suggested for why allopathic physicians sometimes fail is that they know that some people will not respond to their therapies, and they convey this doubt to their patients. An acupuncturist may have an advantage simply because he or she seems certain that a therapy will work, thereby convincing the patient that it cannot fail.

Vertosick (2000) warns: “If our patients can’t imagine a good result, they won’t experience a good result” (p. 269). We should therefore strive to make use of the placebo effect in a completely open manner. This means that we have to get rid of the notion of placebo as deception. The placebo effect is just one example of autosuggestion. So with autosuggestion we may have something that we can use without the need of a placebo—no deception is required.

CONCLUSION

The different explanations of the placebo effect eventually boil down to the concept of autosuggestion (communication to the subconscious). This suggests that the ubiquitous placebo effect is in fact a *covert* kind of autosuggestion. If this is the case, we may have to rethink much of modern regular medicine. Autosuggestion as *overt* communication to the subconscious should probably be in the center of medicine, even if it is not completely understood at present. This means that we may have to deepen our science. At stake are health and well-being of all.

References

Amanzio, M., and F. Benedetti. 1999. Neuropharmacological dissection of placebo

analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci* 19(1):484–94.

Amanzio, M., et al. 2001. Response variability to analgesics: A role for non-specific activation of endogenous opioids. *Pain* 90:205–15.

Barber, T. X., N. P. Spanos, and J. F. Chaves. 1974. *Hypnosis: Imagination and human potentialities.* New-York: Pergamon Press.

Baron, J. 1990. *Thinking and deciding.* Cambridge: Cambridge Univ. Press.

Barrett, B., et al. 2006. Placebo, meaning, and health*. Perspect Biol Med* 49(2):178–98.

Beecher, H. 1955. The powerful placebo. *JAMA* 159:1602–6.

Benedetti, F., C. Arduino, and M. Amanzio. 1999. Somatotopic activation of opioid systems by target-directed expectations of analgesia. *J Neurosci* 19(9):3639–48.

Benson, H., and M. D. Epstein. 1975. The placebo effect: A neglected asset in the care of patients. *JAMA* 232:1225–27.

Benson, H., and D. P. McCallie Jr. 1979. Angina pectoris and the placebo effect. *N Engl J Med* 300 :1424–29.

Bootzin, R. R. 1985. The role of expectancy in behaviour change. In *Placebo: Theory, research and mechanisms,* ed. L. White, B. Tursky, and G. E. Schwarts, 196-210. New York: Guilford Press.

Branthwaite, A., and P. Cooper. 1981. Analgesic effects of branding in treatment of headaches. *BMJ* 282(6276):1576–78.

Brody, H. 2000. *The placebo response.* New York: HarperCollins.

Butler, C., and A. Steptoe. 1986. Placebo responses: An experimental study of psychophysiological processes in asthmatic volunteers. *Br J Clin Psychol* 25:173–83.

Byerly, H. 1976. Explaining and exploiting placebo effects. *Perspect Biol Med* 19:423–36.

Cabot, R. C. 1978. The use of truth and falsehood in medicine. *Conn Med* 42:189–94.

Churchland, P. S. 2002. *Brain-wise: Studies in neurophilosophy.* Cambridge: MIT Press.

Churchland, P. S., and T. J. Sejnowski. 1992. *The computational brain.* Cambridge: MIT Press.

de Craen A. J., et al. 2000. Placebo effect in the acute treatment of migraine: Subcutaneous placebos are better than oral placebos. *J Neurology* 247(3):183–88.

Dennett, D. C. 1992. *Consciousness explained.* London: Penguin.

Ernst, E. 2001. Towards a scientific understanding of placebo effects. In *Understanding the placebo effect in complementary medicine,* ed. D. Peters, 17-30. Edinburgh: Churchill Livingstone.

Evans, D. 2003. *Placebo.* London: HarperCollins.

Evans, F. J. 1981. The placebo's response in pain control. *Psychopharmacol Bul* 17:72–76.

Evans, F. J. 1985. Expectancy, therapeutic instructions, and the placebo response. In *Placebo: Theory, research and mechanisms,* ed. L. White, B. Tursky, and G. E. Schwarts, 215-228. New York: Guilford Press.

Fisher, H. K., and B. M. Dlin. 1956. The dynamics of placebo therapy: A clinical study. *Am J Med Sci* 232:504–12.

Frank, J. D. 1973. *Persuasion and healing.* Baltimore: Johns Hopkins Univ. Press.

Glaser, R., and J. Kiecolt-Glaser. 1994. *Handbook of human stress and immunity.* New York: Academic.

Gracely, R. H., et al. 1985. Clinicians' expectations influence placebo analgesia. *Lancet* 84(19):43.

Grevert, P., and A. Goldstein. 1985. Placebo analgesia, naloxone, and the role of endogenous opioids. In *Placebo: Theory, research and mechanisms,* ed. L. White, B. Tursky, and G. E. Schwarts, 332-350. New York: Guilford Press.

Grünbaum, A. 1984. *The foundations of psychoanalysis: A philosophical critique.* Berkeley: Univ. of California Press.

Hahn, R. A. 1985. A sociocultural model of illness and healing. In *Placebo: Theory, research and mechanisms,* ed. L. White, B. Tursky, and G. E. Schwarts, 167-195. New York: Guilford Press.

Herrnstein, R. J. 1962. Placebo effect in the rat. *Science* 138:677–78.

Hoffman, G. A., A. Harrington, and H. L. Fields. 2005. Pain and the placebo: What we have learned. *Perspect Biol Med* 48(2):248–65.

Holland, H. Z., and P. Guerra. 1998.A conversation with J. Frank. *Counseling Today.* http://www.counseling .org/ctonline/archives/ct0898/frank.htm

Houston, W. R. 1938. The doctor himself as a therapeutic agent. *Ann Intern Med* 11:1416–25.

Johnson, A. G. 1994. Surgery as placebo. *Lancet* 344:1140–42.

Jospe, M. 1978. *The placebo effect in healing.* Lexington, MA: Lexington Books.

Kirsch, I. 1985. Response expectancy as a determinant of experience and behaviour. *Am Psychol* 40 :1189–1202.

Lasagna, L., et al. 1954. A study of the placebo response. *Am J Med* 16:770–79.

Laska, E., and A. Sunshine. 1973. Anticipation of analgesia a placebo effect. *Headache* 13:1–11.

Levine, J. D., N. C. Gordon, and H. L. Fields. 1978. The mechanism of placebo analgesia. *Lancet* 2:654-657.

Levine, J. D., et al. 1979. Role of pain in placebo analgesia. *Proc Nat. Acad Sci USA* 76 :3528–31.

Markus, H. 1983. Self-knowledge: An expanded view. *J Personality* 51:543–65.

Marr, D. 1982. *Vision*. New York: W. H. Freeman.

Mayberg, H. S., et al. 2002. The functional neuroanatomy of the placebo effect. *Am J Psychiatry* 159:728–37.

Miller, F. G., L. Colloca, and T. J. Kaptchuk. 2009. The placebo effect: Illness and interpersonal healing. *Perspect Biol Med* 52(4):518–39.

Moerman, D. 2002. *Meaning, medicine and the "placebo effect."* Cambridge: Cambridge Univ. Press.

Moerman, D. E., and W. B. Jonas. 2002. Deconstructing the placebo effect and finding the meaning response. *Ann Intern Med* 136(6):471–76.

Mommaerts, J.-L. 2000. *Genees jezelf. [Heal Yourself].* Lannoo: Tielt.

Pavlov, I.P. 1927. Conditoned reflexes. London: Routledge and Kegan Paul.

Peck, C., and G. Coleman. 1991. Implications of placebo theory for clinical research and practice in pain management. *Theor Med* 12:247–70.

Plotkin, W. B. 1985. A psychological approach to placebo: The role of faith in therapy and treatment. In *Placebo: Theory, research and mechanisms,* ed. L. White, B. Tursky, and G. E. Schwarts, 237-254. New York: Guilford Press.

Price, D. D., and H. L. Fields. 1997. The contribution of desire and expectation to placebo analgesia: Implications for new research strategies. In *The placebo effect: An interdisciplinary exploration,* ed. A. Harrington, 117-137. London: Harvard Univ. Press.

Price, D. D., et al. 2007. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain* 127(1–2):63–72.

Reiss, S. 1980. Pavlovian conditioning and human fear: An expectancy model. *Behav Ther* 11:380–96.

Richardson, P. H. 1994. Placebo effects in pain management. *Pain Rev* 1:15–32.

Ross, M., and J. M. Olson. 1981. An expectancy-attribution model of the effects of placebos. *Psychol Rev* 88:408–37.

Sarno, J. E. 1998. *The mindbody prescription: Healing the body, healing the pain.* New York: Warner Books.

Shapiro, A. K., and L. A. Morris. 1978. The placebo effect in medical and psychological therapies. In *Handbook of psychotherapy and behaviour change: An empirical analysis,* 2nd ed., ed. S. L. Garfield and A. E. Bergin, 369-410. New York: Wiley.

Shapiro, A. K., and E. Shapiro. 1997. *The powerful placebo.* Baltimore: Johns Hopkins Univ. Press.

Shumaker, J. F. 1991. Introduction. In *Human suggestibility,* 1-33. New York: Routledge.

Smith, G. R., and P. McDaniel. 1983. Psychologically mediated effect on the delayed hypersensitivity reaction to tuberculin in humans. *Psychosom Med* 45:65–70.

Spiro, H. 1998. *The power of hope: A doctor's perspective.* London: Yale Univ. Press.

Vertosick, F. T. 2000. *Why we hurt.* Orlando: Harcourt.

Wall, P. D. 1993. Pain and the placebo response. *Ciba Foundation Symposium*

174:187–211.

White, L., B. Tursky B., and G. E. Schwarts. 1985. *Placebo: Theory, research and mechanisms.* New York: Guilford Press.

Zeki, S. 1993. *A vision of the brain.* Oxford: Blackwell.

From Placebo to ‘Open-Label Placebo’ to Open Altogether

This article discusses administering a placebo while being open about its nature, the incompatibility of openness with the intent of a placebo to deceive, and the possibility of using the underlying mechanisms of placebos without actually using placebos themselves. The article contends that openness and deception are contradictory by definition, and therefore the fundamental issue is what can be achieved using these underlying mechanisms in an open way. In light of the concepts discussed in the preceding two articles, it becomes apparent that the scope for doing this is quite significant.

4.6 FULL ARTICLE: From Placebo to 'Open-Label Placebo' to Open Altogether

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Submitted in: "PLOS One"

Abbreviations: Open-label placebo (OLP); irritable bowel syndrome (IBS); attention deficit & hyperactivity syndrome (ADHD)

Keywords

placebo effect, placebos, complementary therapies, empathy, informed consent, psychosomatic medicine

Abstract

Scientific medicine has become scientific some 200 years ago in order to move beyond magic, but placebos are essentially 'magical'; they deceive a patient into thinking "this potion is effective for me" when it isn't. Open-label placebos (OLPs) are a welcome effort to find an ethical solution to this problem. With OLPs, patients are given a placebo, but are told openly that they have received one. However, the more open the process, the less the term 'placebo' applies. Once there is complete openness, there is no 'placebo', but rather something that symbolizes empathy to the patient. The most ethical approach here is to strive for complete openness. Subconceptual communication and autosuggestion take us in this direction.

Article

The powerful placebo is fact, and yet it is by definition a deception. In the final analysis, it is the patient himself who is 'effective'. As a consequence, placebos are under ethical scrutiny, and rightly so [1]. Scientific medicine became scientific in order to move beyond magic, but placebos (as clearly differentiated from empathy) [2] are 'magical'; they deceive a patient into thinking that a potion, pill, or surgery actually treats their ailment, when in fact it does not. Moreover, placebos do not

tackle underlying causes. They only offer shallow comfort at the expense of human insight, and do not lead to meaningful subconscious processing.

Today, we have evolved far beyond a Freudian understanding of the subconscious, with cognitive neuroscience providing a wealth of data in support of a more modern view. However, there is a profound ignorance of these data in scientific medicine, leading to a tremendous tension that has consequences for all aspects of psychosomatics. The placebo is only one example. Others arise from the burgeoning set of functional disorders for which satisfactory solutions are rarely available. Many psychotherapeutic treatments have been shown not to act through the theoretical underpinnings which they claim. Psychopharmacological 'solutions' can make matters worse; for example, chronic insomnia patients who take benzodiazepines daily for more than a few weeks can experience rebound phenomena when they stop. Drugs can also lead to functional pain syndromes – for example, pain hypersensitivity from chronic morphine use [3] – and even depression, due to the substantial placebo effect of antidepressants [4]. Worst of all, there is a flood of placebo-based medicine under the guise of 'Complementary & Alternative Medicines' (CAMs), clearly demonstrating that *a lack of rational solutions* invokes the ever-present and unfortunate – but ultimately understandable – human tendency to regress into magical thinking.

Open-label placebos (OLPs) are a welcome step towards an ethical solution for this problem [5]. With OLPs, patients are given a placebo, but are told openly that they have received one. This approach has been shown to be effective in some studies. For example, in a study by Kaptchuk et al. involving 80 IBS patients, an OLP approach was taken, with the result that the "*% of patients reporting adequate relief during preceding 7 days at day 21 endpoint (59%) was comparable with the responder rates in clinical trials of drugs currently used in IBS.*" [5]

In another OLP study by Sandler et al that involved 70 children with ADHD, one group received a full dose of medication, while another received a full dose initially, but were given a dose from the 5th week that was half active medication and half placebo – described as a 'dose extender'. After 8 weeks, there was no difference in how well ADHD symptoms were controlled between the two groups [6].

These OLP studies examine an intriguing premise: a 'placebo without deception'. While this idea has huge ethical merit, there is a need to delve deeper into what is precisely going on here. Specifically, when is something a 'deception'? For instance, could the people in these studies believe consciously or subconsciously that they did

not receive a placebo, and think instead that the study is about the effects of disguising an active medication as a placebo? Do they really understand what a placebo is – even after they are told – and do the physicians themselves understand? Are the patients influenced by seeing "it work" in others?

To be blunt, saying "it works" is not truthful, since "it" doesn't work. What works is not the sugar pill, but the complex psychosocial milieu and ultimately the patient himself. Calling the sugar pill a placebo in these cases may also be untrue, due to people's connotations. In fact, the really important characteristic in this may be *openness*; with proper openness, the patient is in full control. He then *uses* the sugar pill as something completely different; it is no longer a 'closed-label placebo' – which is how the term 'placebo' is used generally. Therefore, we assert that it is important to reserve the term 'placebo' for something that *by definition* involves deception. Given this, a 'placebo without deception' is a contradiction in terms. This more precise definition also clarifies the OLP premise; when OLPs are taken to their logical conclusion, they are no longer placebos.

As a further clarification, consider a Native American ritual that is performed by someone within this culture who believes in the ritual genuinely and profoundly. From a strictly rational viewpoint this is not completely open, but it is as open as possible *in view of the circumstances*. Therefore it is no deception, no placebo, but a cultural phenomenon that needs to be deeply respected; it is perfectly ethical. However if the same person just 'went through the motions' with little personal involvement, in order to get symptomatic relief or other personal benefit, then the ritual is a placebo and unethical. There is a continuum between these two extremes, but the distinction is clear, as is the lesson: what must be sought is something that is rational but that communicates a deep meaning *at the same time*.

In present-day regular medicine, the exclusively rational is triumphing over the meaningful, but the deceptive placebo is a dark reminder that we, as humans, need both. OLP is moving in the right direction; the crux of its approach lies in the surrounding subconceptual communication – not the information that is overtly communicated, but the unspoken subtext and its associated meaning. In truth, this shows that such communication is important with *any* medication. One can take a painkiller and say "I need this pill. My mind plays no role in this at all. Next time I have pain, I will need a painkiller again." This is very different from saying "Doing this has the effect I want to achieve. I also know that this is partially a placebo, so I *can in principle* achieve results just with my own mind." Adopting this stance when

taking medication is wrongfully overlooked; it has the potential to heighten the placebo effect while lowering the associated deceit.

Taking this one step further, placebos would not be needed if a rational and open means of subconceptual communication or 'autosuggestion' could be found [2,7]. This would be an ethical endeavor in support of openness, respect, human insight, free choice and trust. Furthermore, we should be more open to the reality of our brain. This is not philosophical 'materialism'. The real question is whether we look at our mind as being devoid of meaning or replete with it. One can throw away every single molecule in the brain; nothing is left and yet no meaning can be found in any constituent molecule. One can do the same with any work of art and not find 'art' – and yet art is the heart of the piece. Taking a purely material view of the brain is equivalent to denying the existence of art, which is extremely short-sighted. We do not imply that this defines where meaningfulness begins or ends, only that meaningfulness has huge implications in sickness and in health. The placebo effect may only be the tip of the iceberg.

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Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest'

References

1. Benedetti F. The placebo response: science versus ethics and the vulnerability of the patient. World Psychiatry 2012;11:70-72

2. Mommaerts JL, Goubert L, Devroey D. Empathy beyond the conceptual level. Perspect Biol Med 2012;55:175–182

3. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. J Pain 2009;10:316-322

4. Kirsch I. The Emperor's New Drugs. London: The Bodley Head, 2009:226

5. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLOS One 2010;5:e15591

6. Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? J Dev Behav Pediatr 2010;31:369-375

7. Mommaerts JL, Devroey D. The placebo effect: how the subconscious fits in. Perspect Biol Med 2012;55:43-58

Placebos have many ‘side-effects’

This article asserts that if the ‘placebo situation’ – the placebo itself along with accompanying environmental factors – actually works, then it is likely that it also has side effects. Many of these can be easily identified. In view of these negative effects, we urge that placebos only be used with extreme caution. The assertion that “At least a placebo does no harm” is *very* wrong, as is the premise that it is all right for just anyone – whether qualified or not – to use autosuggestion. This area is in urgent need of further investigation.

4.7 FULL ARTICLE: Placebos have many 'side-effects'

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Submitted in: "PLOS One"

Keywords

placebo effect, placebos, complementary therapies, empathy, informed consent, psychosomatic medicine

Abstract

There is a general idea that placebos are harmless, and yet the power of the placebo is a fact. If something is powerful, it can harm. Confusion arises when that harm is not sought at the same level as the effect, namely the level of plain sugar versus the level of deeper meaning and expectations. The latter makes the placebo also an ethical issue. Once one does start to investigate the correct level, one can discern many 'side-effects' in a broad sense. The most important of these may be the violation of truth and what this engenders inside a person who is 'deceived' by a placebo. The question of whether or not to allow the use of placebos in any form to ameliorate symptoms therefore touches in a profoundly ethical way the deepest aspects of what it means to be human.

Article

Many people, including caregivers, think pure placebos are harmless, since "they have no active ingredients." It is true that a pure placebo – be it pill or potion – has no *pharmacological* effect and therefore no *pharmacological* side-effects (note that this is different from a nocebo [1]). However, the *power of placebo* is a fact [2]. That power does not derive from the sugar in the pill but from the broader psychosocial context in which it is administered. In the end, what 'works' in the placebo phenomenon is the deep meaning to the patient – their hopes, beliefs and expectations. Whether and how to acknowledge and use this deep meaning is arguably the most important ethical issue in medicine.

One can look into the brain and see this effect of meaning. For instance, with an analgesic placebo, there are visible and varied consequences, including endorphin release [3]. Since meaning clearly has effects [4], it can in a broad sense also have 'side-effects' at many biopsychosocial levels. This should be taken into consideration when considering placebo use – for example, the current debate in Germany about whether to recommend the use of pure placebos in clinical practice [5]. It is also an issue when a recommendation committee finds a complementary and alternative medicine (CAM) depends largely or totally on the placebo effect – leaving aside the empathy of the caregiver. In fact, many recent relevant studies of CAMs make the conjecture – which is probably very wrong – that "at least there is no harm involved", a position that CAM organizations are also increasingly adopting.

This assumption that placebos are harmless is related to a confusion found in many current placebo debates. When one looks at a pure placebo merely as 'sugar', there are by definition no (major) side-effects. However, when looking at it as *powerful placebo*, one *must not* only look at the sugar inside. Its side-effects must be investigated with the same rigor that its effects are. One must not be lead astray by these two different definitions. The remainder of this text is a list of topics that may be used for a comprehensive study of the real and important side-effects of placebos.

Comparing 'placebo' to 'empathy', one can see that both are related to 'meaning' – or 'deep meaning', to distinguish this from a superficial definition of the term 'meaning'. So, placebos and empathy are related to each other – and sometimes confused – but ethically they are total opposites. Placebos are by definition a kind of deception, whereas empathy is by definition very open and therefore incompatible with deception. Of course, one can administer a placebo out of compassion in a desperate situation, but when placebos are used for the long run – as in functional syndromes such as chronic pain or depression – they diminish empathy due this mutual incompatibility. Physicians who use placebos frequently do not have open relationships, especially if they use placebos to get rid of 'annoying' patients and situations or, even worse, use them to enhance their status as a caregiver without developing empathy. This is particularly unfortunate, since empathy can make the use of placebos unnecessary in the first place.

In the end, and going beyond the Cartesian distinction between mind and matter (in which indeed physiological effects can be seen, as in Parkinson's syndrome [6]), the 'placebo as a lie' can only diminish symptoms, taking away attention from

underlying psychological and medical problems that continue to fester and become very costly, both for the individual and for society. One sees this in the burgeoning numbers of psychosomatic (or 'functional') diseases. These tend to be much more costly to diagnose and treat than somatic diseases. In case of children, taking away such due attention may be especially disconcerting.

A deep feeling of helplessness is one of the most important etiologic factors in psychosomatic disorders [7]. Placebos make deceptive use of a person's own inner strength, and so are not just any deception. They act at a profound level where psychosomatic health and illness are forged. They prevent people from looking consciously to their own inner strength, and so exacerbate their sense of helplessness. They entice the patient into thinking that there must be "something else" that can help them, so that they take what is apparently the easiest route, rather than taking responsibility for their own health. This creates an every-increasing dependency on placebos, which, ironically, is a major factor in the commercial success of 'placebo-based medicine', as is the case for many CAMs. All of this makes placebos a deeply ethical concern, as it goes to the root of self-respect.

Placebos also lead to an acute loss of confidence when people find out that they have been given a placebo under the guise of genuine therapy. This can be personal ("I have been deceived"), group-based ("The caregiver in this village is a deceiver") or very broad ("This governmental organization reimburses quack medicine"). This loss of confidence can be conscious or subconscious, in either case leading to substantial consequences.

Without going into each of them in more detail, a non-comprehensive list of further possible 'side-effects' that need to be investigated are as follows: people losing confidence in medical science if scientists generally accept the deception of placebos; placebos promoting anti-science – leading to a spiraling conflict with rationality and science; patients forcing or urging their caregivers to give them 'something' that fulfills the same promise as a specific placebo-based treatment; a reduction in the effect of regular medications due to people not knowing whether they are receiving an active treatment or a placebo – with doubt creating a nocebo effect; wasting potential caregivers' time and energy by educating them about placebo-based medicines rather than developing their empathy skills; placebos becoming a legally objectionable deceit in view of patient consent (a patient cannot consent to being deceived in clinical cases of placebo use– it wouldn't even 'work', nor does it work with *open label placebos* [8], insofar as these are really 'open', i.e.

'non-deceitful' [9]); people becoming vulnerable to quacks of all kinds, including those outside of the domain of medicine; the material side-effects of the placebo vehicle itself; failure to diagnose real diseases; the sheer monetary cost of placebos under our hypothesis that 'a lie can never provide deep treatment'; the negative cultural consequences of placebos discouraging introspection; anger arising from the debate between the "I do feel it work!" and "It is completely irrational!" camps; a reduced ability of caregivers who reject the deceit of placebos to make a decent living; the disappointment and sense of betrayal in those who find out after many years that they have been administering pure placebos, which they absolutely would not have done if they knew – and who is going to admit to them that they knew about this all along but still encouraged them?

We urge a thorough investigation of these and other possible side-effects of placebos, whether they are pure or impure. However, we think that these first steps should convince policymakers to be careful when considering placebo recommendations or funding reimbursements. One last side-effect – but by no means the least – is simply the deliberate violation of truth. In the final analysis, that is not acceptable in the domain of health and healing, since it is a violation of what the *powerful placebo* proves above all: 'meaning' has a huge power to heal psychosomatic illness and that power naturally resides within all of us. In the end, only truth can truly cure. This lends the phrase "getting better" deep significance in both health and ethics.

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References

1. Colloca L, Finniss D. Nocebo effects, patient clinician communication, and therapeutic outcomes. JAMA 2012; 307: 567-568

2. Kisaalita NR, Roditl D, Robinson ME. Factors affecting placebo acceptability: deception, outcome, and disease severity. J Pain 2011;12(8):920-928

3. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Arch Gen Psychiatry 2008;65:220-231

4. Moerman D. Meaning, medicine and the 'placebo effect'. Cambridge: Cambridge University Press, 2002

5. http://www.cbc.ca/news/health/story/2011/03/31/placebo-effect-doctors-prescribe.html

6. Benedetti, F, Carlino E, Pollo A. How placebos change the patient's brain. Neuropsychopharmacology 2011;36:339-354

7. Camacho EM., Verstappen SM, Symmons DP. Association between socioeconomic status, learned helplessness, and disease outcome in patients with inflammatory polyarthritis. Arthritis Care Res (Hoboken) 2012;64:1225-1232

8. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One 2010;5:e15591

9. Mommaerts JL, Devroey D. 2013. Placebo to 'Open-label placebo' to open altogether. [accompanying article]

Empathy Beyond the Conceptual Level - Core Nonspecific Factors of Psychotherapy

This article deals with why conceptual insight is not enough for empathy to really ‘work’. Empathy needs a close but respectful connection between the empathizer and the recipient of empathy. This interaction must be almost intimate and needs to transcend the purely conceptual level. Because of this, the difficulty of providing effective empathy is grossly underestimated, as well as its effectiveness. Together with autosuggestion, this kind of empathy will become a critical component of future healthcare.

4.8 FULL ARTICLE: Empathy Beyond the Conceptual Level - Core Nonspecific Factors of Psychotherapy

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ABSTRACT The human mind contains much more than concepts. By only taking into account the conceptual level, a cared-for person may feel utterly lonely and abandoned, not deeply in contact with the caregiver, not deeply understood for who he or she really is. A chronic pain patient, for instance, may react to a purely conceptual-level communication, with its lack of deeper contact, by an increasing sense of loneliness. This in itself may substantially contribute to the suffering of chronic functional pain or even functional disorders in general. In dealing with chronic pain patients, as with any patients, it is therefore very important to develop a sense of empathy that goes beyond this, towards deeply understanding the patient as complete person. This sheds a profound light on the all-important nonspecific factors of psychotherapy, which according to many researchers form the only profoundly active principle in psychotherapy.

THERE IS QUITE SOME CONFUSION in scientific literature about empathy. Generally, *empathy* means the ability to understand another person's feelings, thoughts, and motives cognitively and affectively. The related concept of *altruism* involves a pro-social motivation directed toward the ultimate goal of increasing the welfare of the other person (Batson et al. 1991). However, people may be "altruistic" for many reasons, some of which are rather egoistic. For example, one may project one's own ego at a purely conceptual level into a cared-for person, after which caring for the other becomes a form of caring for the projected ego.

Although altruism clearly does not in itself necessarily transcend egoism, a chronic pain patient, for instance, may not be aware of this. Behind the screen of conscious awareness, he or she may react to a purely conceptual-level communication, with all its lack (and even negation) of deeper contact, by an

increasing sense of loneliness. This in itself may bring even more pain. For the caregiver too, a purely conceptual-level communication may for the same reason bring increased negative affectivity and distress, including feelings of guilt and guilt-projection, if the other does not want to fully comply with being cared for this way (Goubert et al., 2005). Therefore, in dealing with chronic pain patients, it is very important to develop a sense of empathy that goes beyond the conceptual level and that moves towards "deeply understanding" the patient as a complete person. At the level beyond the conceptual level—the level at which concepts alone are principally inadequate to denote what is said, meant, felt, or done—a feeling of loneliness may drastically change into a feeling of connectedness, of being validated and understood for who one really is, transcending egoism.

This notion of empathy beyond the conceptual level sheds a profound light on the all-important "nonspecific factors" of psychotherapy, which according to many researchers form the only profoundly active principle in psychotherapy (Ahn and Wampold 2001; Kirsch 2005; Patterson 1985; Wampold 2001;). These factors can now be defined as "empathy beyond." In retrospect, it may have been difficult to conceptualize these factors precisely because they are principally beyond the conceptual level. For that reason, the search to conceptualize them may even be counterproductive. In this article, we describe at a meta-level what "empathy beyond" is and why it is important, without attempting an exact description. To clarify this endeavor, chronic pain is taken as an example domain.

THE CONCEPT OF EMPATHY IN SCIENTIFIC LITERATURE

With quite a lot of definitional variety and even confusion in the literature about empathy, there is a huge disagreement about what empathy really means. The following are some of the many definitions to be found:

- "The ability to understand the patient's experiences and feelings accurately, it also includes demonstrating that understanding to the patient." (JL Coulehan, cited in Mathiasen 2006, p. 1789)
- The ability to share the other's feelings, in at least two ways: (1) empathy with the pain of another person activates part of the neural pain network (AI, ACC) of the empathizer (in other words, one shares the other's feelings in an embodied manner) and ; (2) cognitively inferring about the state of the other person: "theory of mind" or "cognitive perspective taking." (Hein and Singer 2008)

- "Empathy is about *a sense of* knowing the personal experience of another person, with cognitive, affective and behavioral dimensions." (Goubert et al. 2005, p. 285; emphasis added)
- "Putting oneself in another person's shoes and getting a sense (i.e. cognitive-emotional grasp) of that person's perspective and what he or she is experiencing, feeling, and thinking." (Banja 2006, p. 265)
- "A phenomenon wherein I imagine not what this experience would be like for me, but rather what it would be like as if I could live in this other person's world and feel and interpret that person's experiences as he or she does." (Carl Rogers, cited in Banja 2006, p. 265)
- "A necessary condition for therapists attempting to help others." (Carl Rogers, cited in Goubert et al. 2005, p. 285)
- "The act of correctly acknowledging the emotional state of another without experiencing that state oneself." (Leading group from the Society for General Internal Medicine, cited in Halpern 2003, p. 670)
- "Purely cognitive, contrasting it with sympathy. Sympathetic physicians risk overidentifying with patients . . . clinical empathy should be based in detached reasoning." (Halpern 2003, p. 670)

Underlying these definitions, *empathy* is mostly regarded either as something that happens mainly at the consciously conceptual level, or as something that one can, in a second move, readily and accurately grasp at this level, thereby being able to label the distinct thoughts, feelings, or motives involved, and to communicate these back to the patient or to others. The model of detached concern, which was until a few decades ago still ruling the waves of empathy, presupposes that knowing how the patient feels is no different from conceptually knowing in which distinct emotional state the patient resides (Halpern 2003).

Fortunately, however, in recent decades an evolution has taken place beyond this understanding. Halpern (2003) asserts that: "the function of empathy is not merely to label emotional states, but to recognize what it feels like to experience something. That is why empathy is needed even when it is quite obvious what emotion label applies to a patient" (p. 671). Also, the emphasized words "a sense of" in one of the definitions above indicate a sensitivity to the importance of

subconscious, beyond-conceptual processing within empathy (private communication from one of the authors). Times are changing, but sometimes a lot of time is needed for dramatic changes, especially in clinical practice.

EMPATHY AND ALTRUISM

In order to more clearly delineate "empathy beyond," it is worthwhile to discuss it in relationship to altruism. The "empathy-altruism model" states that the pro-social motivation evoked by empathy is directed toward the ultimate goal of increasing the welfare of the other person (Batson et al. 1991). However, there are several ways in which "selfless" altruism can be seen as egoism in disguise. For example, altruism may be invoked in order to gain the good feeling oneself that comes with sharing vicariously in another person's joy at improvement (Batson et al. 1991). Similarly, altruism may be invoked in order to relieve the personal sadness that may come from witnessing the sadness of a sufferer with whom one feels empathically related (Cialdini et al. 1987). Furthermore, so-called altruism may be directed toward the goal of obtaining social or self-reward (praise, pride, the feeling-good idea of being altruistic) or toward the goal of avoiding social or self-punishment (guilt, shame; Batson et al. 1988). In addition, altruism may serve as part of "terror management," in which generous behavior is meant to restore the idea that one is living in a meaningful world and to defend the self from the threatening awareness of personal mortality (Hirschberger, Ein-Dor, and Almakias 2008). Finally, feelings of altruism can develop due to features of the self-concept being located outside of the individual and inside related others; this self-other overlap can result from a temporary shift in otherwise established boundaries (Cialdini et al. 1997).

This last hypothesis may also be explained through application of evolutionary principles, namely the concept of "inclusive fitness," which states that individuals do not so much attempt to ensure their own welfare and survival as those of their genes. Interestingly, Cialdini et al. (1997) label the concept of self-other overlap as "nonaltruistic," in order to distinguish it from other forms of "altruism as egoism in disguise":

> When the distinction between self and other is undermined, the traditional dichotomy between selfishness and selflessness loses its meaning. Accordingly, under conditions of oneness, helping should not be considered necessarily egoistic; it can be considered nonaltruistic, however, to distinguish it from the concept of selflessness. (p. 490)

Here lies a very important boundary: if there is nothing but a purely conceptual recognition of oneself in the other person or some aspect of the situation, or a purely conceptual recognition of the other inside oneself, then the accounts of altruism as egoism in disguise are quite accurate. We are in the domain of purely conceptual empathy. However, if there is a self-other overlap or oneness at a sub-conceptual level, then egoism versus altruism, selfishness versus selflessness, lose their habitual meaning. We are in the domain of empathy beyond conceptual-level altruism.

EMPATHY AND THE PERSON WITH CHRONIC PAIN

Conceptual-level empathy has many functions. It is a sine qua non for improving clinical understanding, for reducing misunderstandings, and for handling moral challenges in medicine (Pedersen 2008). These functions should not be overlooked when going beyond. One can thus distinguish two kinds of empathy that are both important for dealing with the person in chronic pain, namely the *conceptual* and the *sub-conceptual*. However, when the involved "altruism" is really egoism in disguise, then empathy can have negative effects. For instance, a physician may underestimate pain in an attempt to cope with his own distress (Goubert et al. 2005), thereby also under-treating the patient or worse—evading contact. Or the physician may overestimate pain by seeing himself in the other and by overreacting or catastrophizing, because she has no direct hold on "her" pain in the patient. The physician can then communicate her overestimation to the patient, who as a result of this also gets the embodied opinion of *more* pain—the more so because pain can be purposeful from the outset at a personal and interpersonal level, eliciting reactions in others that are a substantial and integrated part of the whole experience (Goubert et al. 2005). This is also a situation in which empathy can hurt the empathizer, easily leading to burnout (Loggia, Mogil, and Bushnell 2008).

One can see diverse effects of empathy not only in the case of the physician or psychotherapist, but also in couples where one partner is experiencing chronic pain. Sometimes specific elements of the relationship between the couple can enhance the pain of the partner with chronic pain. This may be the case when pain behavior is rewarded by getting attention, or when feelings of guilt towards the partner heighten tensions, resulting in punishing or "hostile-solicitous" spousal responses, or feelings of chronic aggression towards oneself (Cano, Barterian, and Heller 2008; Newton-John and Williams 2006). These chronic negative emotions may heighten pain. At the other side, with genuine and deeply empathic

communication between partners, such as may be the case when both spouses know chronic pain, both partners may experience fewer depressive symptoms and less pain severity (Johansen and Cano 2007).

EMPATHY BEYOND AND THE NONSPECIFIC FACTORS OF PSYCHOTHERAPY

In search of what works and what doesn't in the domain of psychotherapy, many researchers come to the conclusion that the nonspecific factors are the most important ingredients (Ahn and Wampold 2001). However, what these nonspecific factors really encompass is hardly understood. There is a parallelism with the placebo-effect of medication (Kirsch 2005; Patterson 1985; Wampold 2001). In both, "expectancy" (sometimes denoted as "hope," "trust," or "belief") is deemed to be a very important—or even *the* most important—element (Greenberg, Constantino, and Bruce 2006; Kazdin 2005). The relevant question, then, is whether this expectancy is mainly a conscious, conceptual-level phenomenon, or whether it goes beyond the conceptual level. Thinking about empathy, one can clearly see that empathy as such hardly works if it only reaches the conceptual level. Consider acting, which is also an act of empathy: it hardly works when the actor does not reach beyond the conceptual level. In medical practice, if the physician is only coldly able to label the patient's emotions and cognitions, the patient will not yet feel deeply understood. Also, there is no really therapeutic action present in this kind of interaction. Only when the caregiver goes beyond what can be readily labeled will the patient start feeling "healed" through the relation itself. The belief of the patient in a caregiver or in a therapy only really works when it is a *profound* belief. But instilling—or better, inviting—such a belief can only be done in-depth.

This does not mean a return to psychoanalysis, which has always been an endeavor to conceptualize, and therefore to tone down and away, the sub-conceptual part of man. Nor does it mean a hard-core kind of behavioral therapy à la lettre, which itself is (still for many practitioners, though already less in theory) actually an endeavor to negate, or "black-box away," the sub-conceptual part of humanity. In a sense, empathy beyond means the opposite of both. It is humanistic, but it takes into account very profoundly the fact that human mind is mainly sub-conceptual. There can, in principle, be more healing in an ounce of smiling than in a ton of conceptualization, and a rightly chosen metaphor can go deeper than a thousand schemes. An invitation to deeply be yourself, to discover and realize deeper needs and aspirations or goals, can relieve more chronic pain than a therapy-time of labeling. An appropriate moment of silence can reach further than an hour

of chit-chat. These few sentences may make it seem easy, but empathy beyond is not straightforward to master. It can be developed, but it is not just about learning to use some instruments. Instead, it is about becoming the instrument oneself—about being open to a world of sub-conceptual patterns.

One may think that this may lead to over-involvement with the patient's suffering, leading for instance to burnout. There has as yet not been any specific research into this. However, it seems logical that the negative effects of over-involvement are largely the result of being stuck in the conceptual domain. Sub-conceptual thinking is much more flexible, meaning that there can be quick and deep involvement, but also quick and deep de-involvement.

CONCLUSION

The human mind contains much more than concepts. In only taking into account the conceptual level, a cared-for person may feel utterly lonely and abandoned, not deeply in contact with the caregiver, not deeply understood. A person with chronic pain may feel this loneliness very sharply. Indeed, the loneliness may be part of the affective response to chronic pain, and may even substantially contribute to the suffering of chronic functional pain or even to much broader functional disorders in general. Therefore, in the domain of empathy it is of utter importance to go beyond the conceptual level. This will bring the caregiver into deep contact with the cared-for, and the cared-for into contact with his or her deeper self, thereby relaxing possible tensions between the two levels.

Empathy beyond the conceptual level may be the general principle that one can discern behind nonspecific factors of psychotherapy in general. It goes beyond a kind of altruism derived from a relation between two egos, offering instead a deep-to-deep communication between two complete human beings.

References

Ahn, H. N., and B. E. Wampold. 2001. Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. *J Counseling Psychol* 48(3):251–57.

Banja, J. D. 2006. Empathy in the physician's pain practice: benefits, barriers, and recommendations. *Pain Med* 7(3):265–75.

Batson, C. D., et al. 1988. Five studies testing two new egoistic alternatives to the empathy-altruism hypothesis. *J Perspect Soc Psychol* 55(1):52–77.

Batson, C. D., et al. 1991. Empathic joy and the empathy-altruism hypothesis. *J Perspect Soc Psychol* 61(3):413–26.

Cano, A. A., J. A. Barterian, and J. B. Heller. 2008. Empathic and nonempathic interaction in chronic pain couples. *Clin J Pain* 24(8):678–84.

Cialdini, R. B., et al. 1987. Empathy-based helping: Is it selflessly or selfishly motivated? *J Perspect Soc Psychol* 52(4):749–58.

Cialdini, R. B., et al. 1997. Reinterpreting the empathy-altruism relationship: When one into one equals oneness. *J Perspect Soc Psychol* 73(3):481–94.

Goubert, L., et al. 2005. Facing others in pain: The effects of empathy. *Pain* 118(3):285–88.

Greenberg, R. P., M. J. Constantino, and N. Bruce. 2006. Are patient expectations still relevant for psychotherapy process and outcome? *Clin Psychol Rev* 26:657–78.

Halpern, J. 2003. What is clinical empathy? *J Gen Intern Med* 18(8):670–74.

Hein, G., and T. Singer. 2008. I feel how you feel but not always: The empathic brain and its modulation. *Curr Opin Neurobiol* 18(2):153–58.

Hirschberger, G., T. Ein-Dor, and S. Almakias. 2008.The self-protective altruist: Terror management and the ambivalent nature of prosocial behavior. *Perspect Soc Psychol Bull* 34(5):666–78.

Johansen, A. B., and A. Cano. 2007. A preliminary investigation of affective interaction in chronic pain couples. *Pain* 132(suppl. 1):S86–S95.

Kazdin, A. E. 2005.Treatment outcomes, common factors, and continued neglect of mechanisms of change. *Clin Psychol* 12(2):184–88.

Kirsch, I. 2005. Placebo psychotherapy: Synonym or oxymoron? *J Clin Psychol* 61(7):791–803.

Loggia, M. L., J. S. Mogil, and M. C. Bushnell. 2008. Empathy hurts: Compassion for another increases both sensory and affective components of pain perception. *Pain* 136(1–2):168–76.

Mathiasen, H. 2006. Empathy and sympathy: Voices from literature. *Am J Cardiol* 97(12):1789–90.

Newton-John, T. R., and A. C. Williams. 2006. Chronic pain couples: Perceived marital

interactions and pain behaviours. *Pain* 123(1–2):53–63.

Patterson, C. H. 1985. What is the placebo in psychotherapy? *Psychother* 22:163-69. In *Understanding psychotherapy: Fifty years of client-centered theory and practice.* PCCS Books, 2000.

Pedersen, R. 2008. Empathy: A wolf in sheep's clothing? *Med Health Care Philos* 11(3):325–35.

Wampold, B. E. 2001. Contextualizing psychotherapy as a healing practice: Culture, history and methods. *Appl Prevent Psychol* 10:69–86.

From “Does it work?” to “What is ‘it’?” - Implications for Voodoo, Psychotherapy, Pop-Psychology, Regular, and Alternative medicine

This article addresses the need for a firm scientific understanding of ‘it’ even when ’it works’. Particularly given the transparency of the psyche, deep scientific insight is needed into the nature of ‘it’ – as well as ‘towards what’ we need ‘it’ to act. These are important questions that are seldom asked. With autosuggestion and a deeper type of empathy providing an ‘alternative to alternative medicines’, this area is in need of significant research. For the world of CAM and its many bizarre explanations, this has the potential to become both the strongest repudiation at the theoretical level and the gentlest way out at a practical level.

4.9 FULL ARTICLE: From "Does it work?" to "What is 'it'?" - Implications for Voodoo, Psychotherapy, Pop-Psychology, Regular, and Alternative medicine

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ABSTRACT In this article, a "healing method" (HM) is defined as any method intended to improve health through non-somatic means. For many healing methods, especially within the realm of complementary and alternative medicine (CAM), there is mounting debate over the question "Does it work?" Indeed, this seems to be the primary question for most stakeholders. Yet in light of the well-documented effects of nonspecific factors, particularly empathy and placebo (EP), we contend that the basic question is: "What is 'it'?" Without answering this question, scientific progress is impossible, and research costs will spiral upwards without producing tangible results. Furthermore, it is impossible to characterize the potential side effects of healing methods without a full understanding of the underlying mechanisms through which they act. It is generally acknowledged that many healing methods are sociohistorical artifacts, based on underlying theoretical models that are divorced from established science. There is a need for healing method research that is accommodating of such methods' fluid nature while being congruent with accepted scientific practices—. "It works" is no longer an adequate justification for any healing method, as "it" often turns out to be a combination of nonspecific factors.

Historically, "healing methods" (HMs) have not been based on rational theories. Of the thousands of HMs that have arisen over the ages, only a small number survive today, drawing their power and longevity mostly from their superior ability to act as a placebo within the context of modern-day culture, rather than through any other mode of action.

When it comes to HMs, Western scientific culture has not yet evolved

beyond a pre-scientific stage (Fancher 1995). A scientific analysis of the part played by practitioner/subject empathy and other emotional influences within the healing situation is needed. Furthermore, the question "Does 'it' work?" should be reformulated as "Is 'it' an effective placebo?" Once one accepts that the placebo phenomenon is an essential part of any HM, one must then recognize that no placebo, however effective, can go beyond symptomatic treatment to effect real healing. Therefore, it is also appropriate to reframe the question "Which placebos work best?" as "Which placebos are people most likely to adopt and then continue to use?"

We contend that the combination of empathy and placebo (EP)—so-called nonspecific factors—does indeed play a pivotal role in nearly all HMs, including psychotherapy, voodoo, pop psychology, and the nonmaterial aspects of alternative medicine (also called "complementary and alternative medicine," or CAM). This is backed up by abundant data from several domains (Mommaerts, Goubert, and Devroey 2012). However, there is a lack of EP-related research within current scientific health care, due to many historical, financial, status-related, personal, conceptual, and dualistic reasons. Unfortunately, this gap has been filled by numerous unscientific "alternatives," which now form a major component of the health-care landscape. Therefore, we argue strongly that EP should be investigated explicitly as part of any HM-related research, in order to put the discipline on a firm scientific footing.

Note that we include "pop psychology" as an HM. We use this term to encapsulate the host of mass-marketed, superficial, do-it-yourself HMs that fool people into believing that there is an easy recipe for salvation: "Do this, and you will be happy, rich, and popular." As with other HMs, these approaches rely on EP.

"Does it work?" is a good question when "it" has clearly delineated borders and well-characterized content. For example, the question is meaningful for pharmaceuticals or surgical procedures. However, when we start to address less circumscribed domains, such as psychotherapy or most CAMs, the same question can lead us astray. Discussions end with an emphatic "I can see it work," but without a clear understanding of the nature of "it."

When policymakers ask the question "Does it work?" they are often really concerned with the question "Do people feel it work?" This eventually leads to symptomatic treatment en masse, and underlying causes may continue to fester. Policymakers need to be more concerned with what truly helps at a deeper, more

sustainable level. They must recognize that “What is ‘it’?” is a deeply moral question when it comes to HMs. Patients rely on practitioners to know what “it” is, and practitioners in turn rely on scientists to ask and answer the right questions.

EMPATHY AND PLACEBO

The nonspecific factors associated with psychotherapy are most likely to be a combination of empathy and placebo (EP), regardless of specific theoretical models or schools. However, there is a difficulty with the term *empathy,* as it is used to denote different concepts (Mommaerts, Goubert, and Devroey 2012) The same problem applies to the term *placebo* (Mommaerts and Devroey 2012a). Therefore, it is essential to define each of these terms clearly, and to distinguish between the two.

Here, a *placebo* is defined explicitly as something that works through deceit; the archetype is a dummy sugar pill, given to a patient who believes it is a powerful painkiller. This placebo has a real effect: an fMRI scan of the patient’s brain shows the results. However, this placebo effect is not due to the sugar pill itself, but to the sociocultural meaning that surrounds it, to the suggestions that accompany it, and ultimately to the patient. In contrast to the deceit of a placebo, a modern definition of *empathy* is based on openness (Mommaerts, Goubert, and Devroey 2012). Thus by definition, *empathy* and *placebo* are two completely distinct concepts. Important in empathy is an orientation of the empathic person towards more than what is as such conceptually denotable in the empathized-for person. This is the subconceptual level (Mommaerts, Goubert, and Devroey 2012).

There is a third factor that might, at first sight, appear to be part of EP, and this is the human propensity to respond to a healing situation. Many different cultures have developed unique rituals that embrace this propensity. One cannot call such rituals a true deceit, even if, from a Western scientific culture viewpoint, the underlying motives may appear deceitful. Two health-related examples are voodoo, which we will discuss later in this article, and acupuncture as it was practiced in China 1,500 years ago. The “it” in such a culture (where there is a genuine healing situation) is very different from the “it” in Western scientific culture (a deceitful placebo), even if the same materials and procedures are used.

We contend that EP explains the effects of nearly all HMs. Therefore, each practitioner and researcher should answer the following questions: "In light of what you know, is EP enough to explain how ‘it’ works? If not, why?” This principle also

applies to regular medicine. If a medication is shown to work only as a placebo, then it must be investigated further, and perhaps abandoned. Examples of such medications are non-codeine antitussives and arthroscopic lavage for osteoarthritis of the knee (Moseley et al. 2002; Schroeder and Fahey 2004). In general, it is a warning sign if a treatment’s efficacy decreases significantly under more stringent double-blind conditions (Moher et al. 1998; RMITG 1994; Schulz et al. 1995; Walter, Awasthi, and Jeyaseelan 2005).

In assessment, too, regular medicine must take a critical view at all times. For example, in trials of laser-treatment for angina using blinded and unblinded outcome assessors, Noseworthy et al. (1994) found that effects were exaggerated by 29% to 87%—with an average of 69%—when assessors weren’t blinded. This makes it clear that simply taking results at face value is not enough.

Such results do not show a failure of science, but instead demonstrate the huge importance of rigorous scientific methods. There is a need to scrutinize the statement “‘It’ works” and a corresponding duty to ask the question “‘What’ works?” The same reasoning applies to side effects; saying “‘It’ has no side effects” and “‘It’ works” in the same breath is plainly a logical reference error, since the first “it” and second “it” can be two very different things.

Endorsing the underlying, nonrational theory of a given HM does two things: it denies that which is scientifically obvious, and it lends false credence to a sometimes *very* strange hypothetical explanation. Rather than doing this, any practitioner, MD or not, should have a good knowledge of the basics of EP. Once one leaves behind the question ”Does it work?” there is an alliance possible between those who believe in any HM’s theoretical model and those who point to the power of EP to address human sickness and enhance human health. The conflict then becomes one between those who have a deep respect for patients and those who seek to exploit them.

FROM “DOES IT WORK?” TO “WHAT IS ‘IT’?”

With HMs, patients feel that “it” works, and so it is important to know exactly what “it” is. For instance, is “it” the very concrete words that a Candomblé priestess uses at a *terreiro,* the “deity” that invades the patient through her intercession, or the suggestive atmosphere that surrounds the event? Or is “it” the beliefs, hopes, and expectations of the patient himself? Depending on the underlying hypothesis, relevant research questions and appropriate methodologies can differ greatly.

"It" can be defined as EP + X, where X is the specific effect that is claimed by the underlying theory of any specific HM. This leads to the following possibilities:

- X works: it is scientifically valid.
- X doesn't work at all: it needs to be discarded quickly.
- X enhances the action of EP: further investigation is needed.
- X does more harm than good: people who practice this HM should be stopped.

For example, acupuncture seems to work in a limited number of domains. If acupuncture could be shown to work on even one occasion, then its underlying principles, such as chi and meridians, would be proven. However, if what works is not acupuncture but, for instance, some physiological factor, then acupuncture remains unproven. In fact, the limited domains where acupuncture appears to work are very placebo-prone, as exemplified by nausea in chemotherapy and chronic low back pain that is treated with sham-surgery (Shapiro and Shapiro 1997; Watson 1993). In such domains, even small differences in the amount of placebo influences between two groups can lead to statistically significant results; an experimenter's bias that is transmitted through a blinded practitioner to a blinded patient can have an effect. In view of the "it" question, the conclusion should not be that acupuncture works in this limited set of domains, but rather that results that seem to support acupuncture also have a more straightforward explanation.

When is "Does it work?" a valid research question? In principle, we see the following criteria:

- "It" has no significant negative side effects.
- The nature of "it" is irrelevant.
- There is no need to think about what "it" claims to deliver.
- It is unimportant whether "it" can work better.

These criteria are interrelated. However, we can find no HM that meets any of these criteria satisfactorily. Therefore, we contend that "Does it work?" is not a valid research question for HMs at this time.

VOODOO LESSONS

In the eyes of nonbelievers—CAM practitioners, psychotherapists, regular medicine

practitioners, and homeopaths alike—voodoo's underlying assumptions are totally devoid of reality: it is preposterous to say that "it" is the god-sent power of a voodoo wizard. Yet voodoo works extremely well: "voodoo death" is fact, not fiction. It is an example of "sudden death syndrome," which has been, in many cases, attributed to neural influences on cardiac function, resulting in acute myocardial infarctions and lethal arrhythmias (Samuels 2007). For believers, voodoo is real, even while the actual mechanism appears to be very similar to that behind most HMs.

Voodoo is also interesting in that it demonstrates the enormous power of deep belief when it is shared by practitioner and patient and reinforced by their environment. This is consistent with the fact that several Western 20th-century therapies that used to be endorsed by the medical community but that were later abandoned as pure placebos—for example, glomectomies for bronchial asthma, and levamisole for HSV—had huge placebo effects during the period of time in which they were endorsed (Roberts et al. 1993). Within a belief system, practitioners do their best to surround themselves with like-minded believers and affirming artifacts: friends, congresses and literature, to name but a few. These all add to the practitioner's own belief, which shines out as a beacon to patients. The patients then reflect it back to the practitioner, creating a positive feedback loop.

Thus, in order to be properly assessed, charismatic practices such as voodoo need to be studied in their natural environment. Social context and other associated systems are important, as these enhance the power of belief. If research fails to do this, it can result in unrealistic data about the various elements of "it." For instance, it would be helpful in any HM research discussion to quantify, as far as is possible, the "belief factor," including environment-engendered belief. What is the difference in the results obtained from patients who are full believers, and from those who are nonbelievers? How do results vary between people who approach a procedure in a detached manner, and those who are emotionally engaged? In this last example, detachment could be created by explicitly explaining the procedure to the subjects, or by distracting them.

WHAT DO PATIENTS REALLY WANT?

Usually, research questions are not developed with patients' informational needs in mind. However, with HMs, it may be particularly appropriate to do this. For instance, a survey questionnaire could contain the following:

- Would you care if a specific HM has a lot of side effects?

- What would you think if your practitioner knew the "active ingredient" is not the HM, and you were, in fact, healing yourself?
- Do you think EP is powerful enough to produce the same effects as this HM?

Assuming that patients do not care to be deceived by their HM practitioners, the question "What works?" may seem less important. However, is this correct? Patient consent is incompatible with deception. When a patient agrees to X, there is no real consent if they actually receive Y instead. Based on this, and armed with current knowledge, one can argue that a number of CAMs do not obtain patient consent, and so are illegal.

Patients do not want side effects. That is a major reason for the success of CAMs (Angell and Kassirer 1998; Jonas 1998). In other words, "If 'it' doesn't work, then at least 'it' does no harm." However, this sentence is illogical. If "it" can work as claimed by a specific HM theory, then "it" can definitely have side effects. If one can ask the gods for something good, then they can bring something bad as well. If one can balance chi, then one can also imbalance it. If needles are applied at the wrong acupoints, surely they have the power to make things worse, instead of better. One would expect so, based on theory of yin and yang. On the other hand, if the causal factors associated with "it" are purely psychosocial, then the side effects will also be psychosocial, not physical. This way, placebo-based medicine may have a lot of substantial and relatively unexplored side effects such as diminishment of a sense of deep self-reliance.

INTERNAL VALIDITY AND STANDARDIZATION

HMs are notorious for creating ongoing tension between those who want standardization and those many individual practitioners who feel the urge to do their own thing. Such tension is intrinsic to the "magical" nature of a placebo. For instance, a recent paper by Mathie et al. (2012) examines standardization of homeopathic studies for the purpose of meta-analysis. The suggested criteria (or domains) are very subjective. Who should decide finally? The proposed procedure may inadvertently enforce an internal standardization that is unwanted by homeopaths. Different homeopathies (individualized or not) will support different committees, and some homeopaths will not agree with any of them. Also, if criteria are only developed and imposed upon randomized controlled trials after looking at results, then this is subjective and an invitation to data trawling. It is also noteworthy

that the study proposes no measure of empathy. This is a lack in the vast majority of HM-related randomized controlled trials.

SCIENCE VERSUS BELIEF SYSTEM

Within a belief system, anything can be used as a basis of authority. For HMs, this includes science itself, since it has significant authority within Western scientific culture. However, this results in a contradiction, as HMs strive on the one hand for scientific validation, and on the other hand mistrust science as something that is not qualified to disprove the HM's belief system. For instance, much effort has been devoted to placing randomized controlled trials articles about acupuncture in peer-reviewed journals, but at the same time, it is frequently argued that there is no good acupuncture placebo that can be used in scientific studies or that the studies use invalid blinding mechanisms, and that therefore the results of the studies are not subject to scientific falsification. This is the anti-reductionist "holistic" argument, which leads to an "alternative science." It also allows proponents to claim that their own method has not, at least, been disproven.

The term *holistic* has a huge attraction for HMs, but the outcome criteria are frequently very un-holistic—for example, body weight reduction. An HM that claims such outcomes is not holistic but a placebogenic belief system. The practitioners' investment of time, energy, money, and status only makes their belief stronger. Basic science transcends culture: one cannot say that gravity exists in one place but not in another. The laws of nature are not cultural laws. While each culture has its own ways of eliciting empathy, science *about* empathy is basic. HM practitioners should ask themselves the following question: "If this HM had no history, no supporting organization and no proof, would I still endorse it?"

As in other sciences (such as physics or chemistry), clinical research must not be devoid of theory or a guiding methodology. No reputable biologist says, "I am not a physicist, and therefore the laws of physics do not apply to my science." Neither should any homeopath. However, a belief system brings expectations. Paradoxically, many HMs need to be seen as "more than rational," as this is a major part of their placebogenic lure. This issue needs to be addressed in any HM research, for example by distinguishing between subjects who are at home in a specific subculture and those who are not.

The proponents of CAM systems usually have a strong desire to find scientific proof. "Giving up" means giving up hope, but hope is at the core of the

placebo effect: to give up the search means to give up completely. Believers cannot do that without having an alternative, or they will risk falling into a void. Believers may become even keener to prove their point as they approach the situation where their belief system is about to break down. Individuals who don't experience this risk find the circumstances and motivations of believers hard to appreciate.

MANY OR ONE?

The HM domain exists as a continuum between two opposing poles. At one pole, each HM is an entity unto itself, distinct from the others. Each boasts a specific theoretical model and is placebogenic: it claims "healing" based upon its model, whether or not the model is true. Believers at this pole, both practitioners and patients, are usually intensely loyal to their model. At the other pole, one can treat multiple HMs as a single entity with different appearances. For example, many CAMs taken together can be treated as one (one-entity-CAM); the various models and belief systems of the individual CAMs reside above a deeper, shared layer. Believers at this pole act as if they simultaneously do and do not care for any specific underlying model.

While belief systems are always difficult to falsify, directly invalidating one-entity-CAM is impossible. This belief system can mold itself to people's changing preferences and to differing situational dynamics. To ask the question "Does it work?" is fruitless. If research shows that a particular CAM doesn't work, that CAM often continues unabated in the marketplace without scientific backing, or it transforms itself into a "method plus," with enough differences to justify another round of hype. Even if it does disappear, it is quickly supplanted by another method that appears different, but shares the same foundations.

In the following passages, we discuss some of the efforts taken to test various CAMs.

Dismantling Studies

Many dismantling studies have been performed in a search for the "active ingredients" of psychotherapy (Shapiro and Shapiro 1997). The results are disconcerting, as no element or combination of elements related to underlying theories turns out to be the one that works. Any dismantling leads to a partial therapy that works as well as the full therapy, provided that a minimum level of practitioner/patient interaction is maintained.

The same may be true of any HM. Although some argue that the holistic nature of CAMs means that they cannot be dismantled properly, we do not agree. For example, homeopathic remedies are modular entities; it doesn't matter which pharmacy delivers them. Likewise, acupuncture contains modular elements that can be dismantled from the whole. In general, dismantling seems a valuable research methodology for many HM modules.

Different CAMs can be viewed as elements of one dismantled one-entity-CAM. Taken in this light, different combinations of CAMs that provide the same amount of EP should be equally effective. Conversely, given the varying theoretical models and modes of action of different CAMs, one would expect that a combination of CAMs would have a combined effect. The latter, however, is not reported to be the case.

Turning to acupuncture, the Streitberger procedure dismantles the needles element from the whole; the needles are placed in plastic tubes and touching the skin without puncturing it. According to some researchers, this procedure is also acupuncture (Zheng et al. 2012), but then why did 2,000 years of Chinese wisdom not discover this, preventing many infections and even hepatitis-B epidemics? This is bizarre (Mommaerts and Devroey 2012b). Other rather recent examples of dismantling include auricular and foot sole acupuncture. Here too, if these are as effective as total-body acupuncture, why have they not been discovered in 2,000 years?

Another modern dismantling example can be found in those cognitive studies where acupuncture is used on "phantom" limbs, or on limbs desensitized with local anesthetic (Kammers et al. 2009). This is, in effect, dismantling the patient. The same acupuncturist, with the same EP, treats real and phantom limbs. If both treatments prove to be equally effective, then the theory behind acupuncture is not veridical.

Expectation Assessment

The degrees of expectation in a subject may have an impact on the effectiveness of an HM. To assess this, one could compare how those who believe in an HM respond to treatment, versus those who do not. However, caution is needed with this approach, because a subject's conscious and subconscious expectations can differ. To some extent, different levels of expectation can be "manufactured." For instance, treatment could be given in both uninviting and

inviting environments, or the same procedure could be carried out in a top-rate hospital or in a dilapidated village. Actors in the waiting room could praise the practitioner or make neutral comments, with the same actors playing both roles to eliminate bias.

Hidden Administration

The hidden administration procedure was used by Colloca et al. (2004) with telling effect. Diazepam and painkillers were concealed from the patient and were administered by hidden infusion through an intravenous line. This is the opposite of a controlled double-blind study with placebos, and yet it studies the same effect. Hidden administration procedures may also shed light on HMs in general. For example, patients may be told that needles will be inserted into the acupuncture points used to treat for X, but the needles are actually inserted into those points that are used for Y, from which they also suffer. The patients are then asked about Y, which should be affected, according to acupuncture theory.

A PURE "EMPATHY + PLACEBO" SITUATION

Over the last century, various psychotherapies have been studied, and all have been shown to work equally well when evaluated neutrally. This is called the Dodo effect, with reference to a story in *Alice in Wonderland* where, under the guidance of a dodo bird, all the animals race without an end goal (Ahn and Wampold 2001; Grencavage and Norcross 1990; Luborsky et al. 2002; Wampold et al. 1997). Even a person with no trained psychotherapy skills may have equal effectiveness as a trained psychotherapist with years of experience (Strupp and Hadley 1979). This has led to a search for "nonspecific factors" in psychotherapy, and many researchers contend that the placebo phenomenon plays a major role here (Ahn and Wampold 2001; Fancher 1995; Greenberg, Constantino, and Bruce 2006; Joyce et al. 2006; Kazdin 2005; Kirsch 2005; Patterson 2000; Prioleau, Murdock, and Brody 1983; Shapiro and Shapiro 1997; Wampold 2001). Of course, if models X, Y, and Z have the same effect and the same EP, then either each model contains additional active ingredients that have comparable positive effects, or EP explains the total effect of each model separately. The latter is a pure EP situation.

Now if a double-blind comparison were set up using a contrived pure EP situation, and no difference were then found between this and any other HM treatment, this could mean either that the pure EP situation was just one of many possible treatments, or that EP is the nonspecific and at the same time only effective

factor in all treatments; they all work equally well because they all work on the same basis. For instance, a pure EP situation could be created by using an actor who impersonates an acupuncturist, along with naïve patients. The actor would stick the needles in acupoints of some patients and into non-acupoints of others; at all times, he would maintain the same level of EP. The actor might need to improve his EP skills over time, and his acupuncture skills would need to be excellent, as evaluated by experienced acupuncturists. It wouldn't matter how long it took to achieve this; the point is that when the actor finally reached the point where he could obtain the same ratio of positive outcomes in both cases, acupuncture would be disproven.

The placebo can also be "opened," in the sense that the patient is made fully aware. This is different from the "open-placebo paradigm" (Kaptchuk et al. 2010). In the latter, the practitioner still speaks of "placebo," which brings with it the connotations and thereby placebo-effect, although to lesser degree. What is meant by "opened" here is no longer denoted as a placebo, but as an instrument to use as auto-suggestion. For instance, the patient is made fully aware that what he gets in a bottle is not a homeopathic remedy but just water that he can use to symbolize a remedy. If this works as well as a homeopathic remedy, than that is proof that the material remedy is ineffective.

WHY IS "WHAT IS 'IT'?" IMPORTANT?

This question leads to what may be the most important domain in future medicine. Moreover, It transcends medicine and goes to the core of human being. "It" is deeply meaning-related, in terms of the deeper meanings of things and also in terms of the deeper meaning of human beings as individuals and even as a species. This deeper meaning does not reside at an analogical level, such as when one searches the meaning of a word in a dictionary. It is deeper in the sense that it is mental, it is never fully conscious, and it is a direction more than an entity, therefore it never fully stops on its way to psychological depth. It is definitely not analogical: one thing does not stand for another. Going deeper, one loses track. But deeper meaning is what people live and die for, and also what can make them sick and then healthy again. We see this in a lot of research on many domains, such as AIDS, chronic functional pain, and the placebo effect itself (Barrett et al. 2006; Bower et al. 1998; Goforth et al. 2009; Lewandowski et al. 2005; Moerman 2002).

Deeper meaning is also related to what the term *soul* denotes in religious

and nonreligious contexts alike. Deeper meaning in a psychosomatic context is compatible with both religion and atheism, while it definitely transcends medicine. Should we then as caregivers interfere with this level of deeper meaning? I think this is the wrong question since we cannot but interfere. The patient comes to the consultation room with his full reality. In cases where a patient’s health deteriorates from a source “deeper” inside himself, as is generally the case in psychosomatics, then whatever a caregiver does interferes with this.

Empathy and the power behind placebo denote two ways to influence the deeper, subconceptual layers of human psyche. Both play an important role in any consultation. If they were two medications, they would be the most important ones in our pharmacopeia, regarding cases used, efficiency, and meaning-relatedness (thus ethical). They are surely worth full and open attention, which includes—wherever possible—not hiding them behind any placebo-screen.

One can see in an urge for openness a deeply ethical endeavor. When deeper meaning is involved, ethics by itself makes the question “Does it work?” incomplete. A more complete question is: “Does it work towards this or that specific goal?” For instance, the goal of a patient with chronic pain may be “to relieve my pain.” That is straightforward. But what if the patient could sell part of her soul in order to “relieve pain”? should she have the same straightforward goal and go on selling? Or what if some remedy relieves pain but at the same time makes it come back more quickly, brings another symptom instead, or, as in the case of morphine, diminishes not only the feeling of pain but other feelings too?

One can easily see that the “towards” part of the more complete question is inextricably bound with the “it” part. Placebo gives no opportunity in concrete cases to validate any of this, as is seen in the lack of openness that is by necessity a placebo’s fate. But empathy thrives on openness, as does rational science. Indeed, empathy and good science have much besides openness in common, including an aversion for preconceptions and a willingness to put oneself critically in the balance at any time.

Western science should clearly validate empathy and, in so doing, try to heighten it. This is not a straightforward agenda, and much more research is needed. As for placebo, we know that “something works towards something,” and rational scientific medicine requires that we properly investigate what works towards what. More insight in this matter must lead to better tools to cure and heal. Moreover, sticking merely to the “Does it work?” question risks flooding the public airwaves

with responses that yes, "this [CAM, for instance] does work." People who spread such messages may be benevolent, yet their messages are extremely misleading to the consumer. Meanwhile, what disappears is a close connection with the finest and deepest part of ourselves, namely the subconceptual level of deeper meaningful patterns. This connection is fundamentally replaced by an overreliance on materialistic remedies. In its starkest form, this is a clash between "matter" (in psychotherapy, the"purely conceptual") and "soul," between materialism and deepest humanity. People's sensitivity to "matter" goes together with a vulnerability that should not be misused willingly nor inadvertently.

Ongoing efforts of the National Center for Complementary and Alternative Medicine (NCCAM) at the NIH are surely needed. It does not help, however, to publish statements such as this one from September 2012, that "the effects of acupuncture on pain are attributable to two components. The larger component includes factors such as the patient's belief that treatment will be effective, as well as placebo and other context effects" (NCCAM 2012). This statement is, as the reader knows by now, as contradictory as it is misleading. Moreover, the second half of the sentence is tautological. Especially in the domain of HM, a domain by necessity wrought in vagueness, using conceptually correct terms is of utmost importance. Surely many misconceptions would disappear if researchers would be more attentive to this.

CONCLUSION

The history of HMs is the history of the placebo phenomenon. The mysterious nature of placebo has translated itself into numerous HMs over the ages, according to the culture, beliefs, and customs that prevail at a specific place and time. The gods of Egypt and ancient Greece, and those of Amazonian, Mongolian, and Inuit tribes cannot all be endorsed in Western scientific culture, yet they all have been placebogenically "active" and in some cases still are. HM practitioners should consider their own beliefs in this broader context. The ascendency of the strongest—that which is most able to capture people's imagination—has consistently shaped the HM landscape, regardless of culture, as it now does in Western scientific culture. Only in recent history has science been able to (partially) overcome the tyranny of pure imagination, by putting falsification at its center, both for itself and for nonscientific belief systems. As encouraging as this is, scientists must not live in ivory towers, oblivious to the fact that this is an ongoing and incomplete effort. Controversial issues remain. The placebo phenomenon remains

present at the heart of evidence-based medicine in placebo-controlled trials, and psychosomatic therapy, the most common reason for consulting a first-line physician, is vulnerable to the same errors that are found in any HM.

One may rightfully say that CAM represents a failing of scientific medicine, in that CAM seeks to address patients' needs that are lost in the technologically focused interactions of modern medicine. CAM represents many patients' search for empathy. However, if empathy were much more valued within scientific medicine, people would not have to make a choice between empathy and science: they could receive both at the same time. At present, this choice, for many, is real, and it brings a lot of suffering.

"Only truth can truly cure" stands at the same level as *primum non nocere* as an overarching tenet of medicine. Research methodologies must be directed towards the patient-centered question "How can I be helped in a respectful and enduring way?" Deceit is neither respectful nor enduring. Although acupuncture is not deceit within the context of its original culture, it becomes deceit when advocated within Western scientific culture, as it flies in the face of basic science. Western scientific culture needs to develop its own scientific approaches for bringing EP to the patient. At present, when it comes to the topics of health and healing in the psychosomatic domain, science continues to fall between the twin stools of "Does it work?" and "What is it?" To address this moving forward, all HM research needs to include a balanced examination of what "it" is.

In this article, we have pointed to the importance of answering "What is 'it'?" in the HM domain. We urge practitioners to be completely open to the effects of empathy, even if this means stopping their current practices. We need to invest in research that enables a smooth and patient-friendly transition towards profoundly rational EP treatment, research that gives new meaning to the words "Patient, heal thyself."

References

Ahn, H. N., and B. E. Wampold. 2001. Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. *J Counsel Psychol* 48(3):251–57.

Angell, M., and J. P. Kassirer. 1998. Alternative medicine: The risks of untested and unregulated remedies. *N Engl J Med* 339:839–41.

Barrett, B., et al. 2006 Placebo, meaning, and health. *Perspect Biol Med* 49(2):178–98.

Bower, J. E., et al. 1998 Cognitive processing, discovery of meaning, CD4 decline, and AIDS-related mortality among bereaved HIV-seropositive men. *J Consult Clin Psychol* 66(6):979–86.

Colloca, L., et al. 2004. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol* 3(11):679–84.

Fancher, R. T. 1995. Cultures of healing. New York: W. H. Freeman.

Goforth, H. W., et al. 2009. Impact of bereavement on progression of AIDS and HIV infection: A review. *Psychosomatics* 50(5):433–39.

Greenberg, R. P., M. J. Constantino, and N. Bruce. 2006. Are patient expectations still relevant for psychotherapy process and outcome? *Clin Psychol Rev* 26:657–78.

Grencavage, L. M., and J. C. Norcross. 1990. Where are the commonalities among the therapeutic common factors? *Prof Psychol* 21:372–78.

Jonas, W. B. 1998. Alternative medicine: Learning from the past, examining the present, advancing to the future. *JAMA* 280:1616–17.

Joyce, A. S., et al. 2006. Psychotherapy research at the start of the 21st century: The persistence of the art versus science controversy. *Can J Psychiatry* 51(13). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3153746/.

Kammers, M. P., et al. 2009. The rubber hand illusion in action. *Neuropsychologia* 47(1):204–11.

Kaptchuk, T. J., et al. 2010. Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS One* 22;5(12). http://www.ncbi.nlm.nih.gov/pubmed/21203519.

Kazdin, A. E. 2005. Treatment outcomes, common factors, and continued neglect of mechanisms of change. *Clin Psychol* 12(2):184–88.

Kirsch, I. 2005. Placebo psychotherapy: Synonym or oxymoron? *J Clin Psychol* 61(7):791–803.

Lewandowski, W., M. Good, and C. B. Draucker. 2005 Changes in the meaning of pain with the use of guided imagery. *Pain Manag Nurs* 6(2):58–67.

Luborsky, L., et al. 2002. The dodo bird verdict is alive and well-mostly. *Clin Psychol* 9:2–12.

Mathie, R. T., et al. 2012. Method for appraising model validity of randomised controlled trials of homeopathic treatment: Multi-rater concordance study *BMC Med Res Methodol* 12:49.

Moerman, D. 2002. *Meaning, medicine and the "placebo effect."* Cambridge: Cambridge Univ. Press.

Moher, D., et al. 1998. Does the quality of randomized trials affect estimates of intervention efficacy reported in meta-analysis? *Lancet* 352:609–13.

Mommaerts, J. L., and D. Devroey. 2012a. Acupuncture for IVF: Do not let needles stand in the way of empathy. *Fertil Steril* 97(5):e26.

Mommaerts, J. L., and D. Devroey. 2012b. The placebo effect: How the subconscious fits in. *Perspect Biol Med* 55(1):43–58.

Mommaerts, J. L., L. Goubert, and D. Devroey. 2012. Empathy beyond the conceptual level. *Perspect Biol Med* 55(1):175–82.

Moseley, J. B., et al. 2002. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 347(2):81–88.

National Center for Complementary and Alternative Medicine (NCCAM). National Institutes of Health (NIH). 2012. Acupuncture may be helpful for chronic pain: A meta-analysis. Research spotlight, Sept. 10. http://nccam.nih.gov/research/results/spotlight/091012.

Noseworthy, J., et al. 1994. The impact of blinding on the results of a randomized, placebo controlled multiple sclerosis clinical trial. *Neurology* 44:16–20.

Patterson, C. H. 1985. What is the placebo in psychotherapy? *Psychotherapy* 22:163–69. Repr. in *Understanding psychotherapy: Fifty years of client-centered theory and practice*. Here fordshire: PCCS Books, 2000.

Prioleau, L., M. Murdock, and N. Brody. 1983. An analysis of psychotherapy versus placebo studies *Behav Brain Sci* 6:275–310.

Recurrent Miscarriage Immunotherapy Trialists Group (RMITG). 1994. Worldwide collaborative observational study and meta-analysis on allogenic leukocyte immunotherapy for recurrent spontaneous abortion. *Am J Reprod Immunol*

32:55–72.

Roberts, A. H., et al. 1993. The power of nonspecific effects in healing: Implications for psychosocial and biological treatments. *Clin Psychol Rev* 13:375–91.

Samuels, M. A. 2007. “Voodoo” death revisited: The modern lessons of neurocardiology. *Cleve Clin J Med* 74(suppl. 1):S8–S16.

Schroeder, K., and T. Fahey. 2004. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev* 18(4):CD001831.

Schulz, K. F., et al. 1995. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 273:408–12.

Shapiro, A. K., and E. Shapiro. 1997. *The powerful placebo*. Baltimore: Johns Hopkins Univ. Press.

Strupp, H. H., and S. W. Hadley. 1979. Specific vs. nonspecific factors in psychotherapy: A controlled study of outcome. *Arch Gen Psychiatry* 36(10):1125–36.

Walter, S. D., S. Awasthi, and L. Jeyaseelan. 2005. Pre-trial evaluation of the potential for unblinding in drug trials: A prototype example. *Contemp Clin Trials* 26(4):459–68.

Wampold, B. E. 2001. Contextualizing psychotherapy as a healing practice: Culture, history and methods. *Appl Prevent Psychol* 10:69–86.

Wampold, B. E., et al. 1997. A meta-analysis of outcome studies comparing bona fide psychotherapies: Empirically, “all must have prizes.” *Psychol Bul* 122(3):203–15.

Watson, M. 1993. Anticipatory nausea and vomiting: Broadening the scope of psychological treatments. *Support Care Cancer* 1(4):171–77.

Zheng, C. H., et al. 2012. Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: A systematic review and meta-analysis. *Fertil Steril* 97(3):599–611.

Causal Thinking in Psychosomatics, with Peptic Ulcer as Case

This article deals with the dire state of causal thinking in medicine, which is responsible for many current gaps in our understanding of a unified body and mind. The situation is so serious that non-conscious mental processing and even the psyche itself may be wrongly eliminated from the equation. Improving the level of causal thinking will not make things easier in practice, but it will lead to the necessity of managing uncertainty while retaining professional integrity. This view presupposes that empathy plays a major role in the relationship between caregivers and patients.

4.10 FULL ARTICLE: Causal Thinking in Psychosomatics, with Peptic Ulcer as Case

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Abbreviations in this article

necessary -causal- factor (NF); peptic ulcer disease (PUD) = peptic ulcer + dyspepsia; Helicobacter pylori (Hp) ; duodenal ulcer (DU)

Abstract

[168 words]

Medical practice as a whole suffers from a lack of clear causal thinking. Prevalent is 'marketplace causal thinking' which straightforwardly looks for 'the cause' of specific health phenomena. Reality however is much more complex. The cause of this dichotomy is itself also complex and related to our understanding of ourselves, 'causality' being a way to define who we are as individuals and as human race. This is mainly about how we 'cause' (= consciously and/or subconsciously meaningfully 'decide') things to happen outside us but also inside us. This way, medical causality and humanity are closely linked. This has ontological as well as ethical implications. Since most medical illnesses are psyche related one way or the other, psychosomatics is a core issue in medical causal thinking. This article aims to show how a simplistic look upon causality deteriorates our view upon the relationship between psyche and soma. A concrete example is the case of Hp, nowadays frequently mentioned as 'the cause' of gastric ulcers *in place of* psychosomatic factors.

Nobel Prize Summary of Press Release 2005

Unfortunately, straightforward causal thinking [a case (1) as described infra] is prevalent in medical scientific as well as popular literature. An example can be found

in the wordings, if not in the intended meaning, of the Nobel Prize Summary of Press Release [1]. Some excerpts, boldface by me:

"This year's Nobel Laureates in Physiology or Medicine made the remarkable and unexpected discovery that inflammation in the stomach (gastritis) as well as ulceration of the stomach or duodenum (peptic ulcer disease) **is the result of** an infection of the stomach **caused by** the bacterium *Helicobacter pylori*."

"It is now firmly established that *Helicobacter pylori* **causes** more than 90% of duodenal ulcers and up to 80% of gastric ulcers."

"The discovery that one of the most common diseases of mankind, peptic ulcer disease, **has a microbial cause**, has stimulated the search for **microbes as possible causes** of other chronic inflammatory conditions."

Patterns of Causation

This section contains a number of abstract drawings. 'Iconography' of these drawings:

The end point (a fat dot at the right end of each drawing) is the result of causation, e.g. peptic ulcer disease (PUD).

The bold arrow in each drawing stands for one specific causal element, e.g. 'Hp infection'.

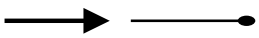
Other arrows stand for other elements, e.g. psychosomatic factors (or other factors such as diet, NSAIDs…) that can play a causal role.

Note that a specific consequence can of course have more 'causal patterns' that stand in an OR-relationship to each other. This is implicitly understood but not incorporated in these drawings.

(1) Direct cause-consequence

('marketplace causal thinking')

HP => PUD

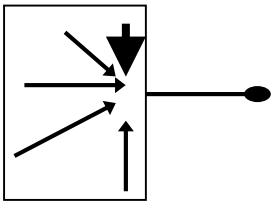


> "*Helicobacter pylori* **causes** more than 90% of duodenal ulcers and up to 80% of gastric ulcers."

This is the most straightforward definition of cause. The strictest interpretation of the predicate 'A causes B' means that both the following are true: 1) A is the *only* cause of B, 2) A *always* causes B.

(2) Causal set

HP + X1 + X2… => PUD

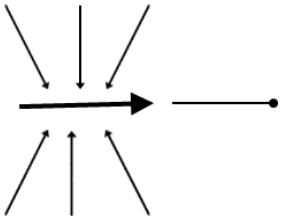


In the case of PUD, possible causal factors are: microclimate within the peptic ulcer or a precursor lesion, Hp, lowered immune defense against Hp, medication, diet, stress, other psychological factors (meanings, expectations…) …

The 'cause' can be seen as a trigger in a domain that has been set (more general cause). E.g. stress may set the situation, in which Hp is then the 'provocative factor'. Hp is then the cause not of peptic ulcer but of *peptic ulcer IN THIS SITUATION*. This shows that the way a research hypothesis is put, is an important determinant for the outcome. For example: '*Antibiotics* cause healing of PUD.' versus '*The use of antibiotics* causes healing of PUD.' versus '*The use of antibiotics in a specific setting* causes healing of PUD.' The 'specific setting' may be one in which the belief in the efficacy of antibiotics is very high. So which concept in italics points to the cause of the healing? In any experiment, only the most specific case is proved, the one with the least confounding factors. However in real-life medicine, the openness of the domain – especially concerning all kinds of psychological factors – is generally not taken into account well enough. The result is an abundance of confounding factors, a huge (and costly) job for falsification and a relatively slow progress of science.

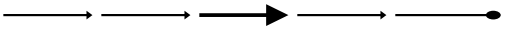
The 'cause' can also be seen as a more general cause in which a trigger may set it to action. E.g. Hp can be present for long periods of time, waiting for a provocative factor. Indeed Hp is present in a large % of the population without PUD. Why do not all these people get peptic ulcers? Clearly an additional factor is needed, such as

possibly an acute distress. A more general 'cause' can also be seen as perpetuating factor. For instance, the finding that early cases of duodenal ulcers are less likely than established ones to be infected by Hp [2], makes this likely to be a perpetuating factor rather than 'the cause'. This can be depicted as infra, in which several other factors may have an influence on the 'main cause'



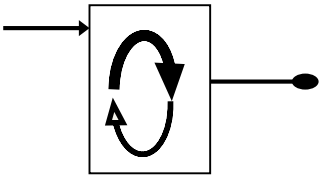
(3) Causal chain

X1 => X2… => **HP** => X4… PUD



Actually, there is no really primary cause for anything. There is always a 'cause of the cause', except (maybe) at the beginning of time. Elements in the chain can be material, psychological, sociological, historical, phylogenetic, etc, in endless chains or patterns. Therefore, denoting anything as thé cause in this chain is nothing but an a priori decision. This way it is easy to prove that all 'real causes' are material as well as it is easy to prove that all 'real causes' are psychological.

(4) Self-enhancing pattern as cause

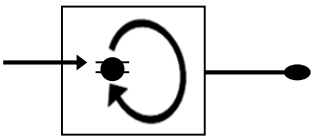


Here we have a pattern containing one or more vicious circles. E.g.: practically no other bacteria can survive in a peptic ulcer environment. Hp has found a perfect niche. By changing the milieu in the ulcer (depicted by the arrow below), it favors its own niche. This way, the actual cause of the peptic ulcer is the existence of the vicious circle(s), not one or the other specific element.

In a combination with this, another 'cause' can give momentum to a vicious circle, as indicated in this drawing by the arrow at the top left. E.g. chronic stress may favor this circle through lowering the immune defense against Hp, as well as through heightening acid secretion.

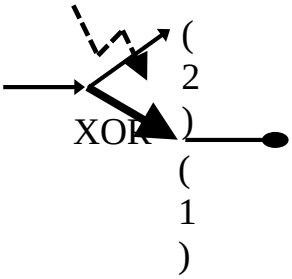
(5) 'Cause' in the non-ending of another 'cause'

This is: the non-ending of something that otherwise does end.



E.g.: Hp waxes and wanes in normal stomachs, probably in a nicely balanced interplay with several other factors such as stomach acidity level. It proliferates into infection when in a period of waxing for instance it is not countered by an appropriate immune or stomach acidity response, as may be caused by an acute stressor.

(6) XOR causality



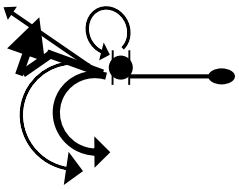
[XOR = 'exclusive OR'; e.g. in 'A XOR B', either A or B can be true but not both at the same time.]

If line (2) is broken, this leads to furthering line (1). Therefore the breaking of (2) is 'cause' of (1). Line (2) may be an outlet for chronic stress

XOR causality becomes more evident when looking at causation of symptoms/diseases in a combined teleological manner instead of a purely etiological manner. This is: as a goal-directed kind of 'communication' that

something needs to be changed. E.g. the pain of a burn 'communicates' to us to be careful with fire. The consequences of a stress-induced situation – such as through immune-deregulation – communicates to us that we should be more careful with leading a stressful life, or develop more 'stressional intelligence', which of course can mean many different things.

(7) Combination of factors



This is in most cases the situation that lies closest to reality, in which any combination is possible. Note the messiness.

Discussion of Causality

In the previous section, we described several patterns in which the 'cause' (e.g. Hp) really behaves as 'cause' in that (1) when taking it away (e.g. through antibiotics), the consequence (PUD) disappears, and (2) when bringing it back through purposefully re-inoculating cured volunteers, that same consequence has a good chance to reappear. Yet in all these cases except the first one, this 'cause' is clearly not the only factor in the causation of the consequence. When one single-mindedly looks for Hp as 'thé cause', one can indeed 'prove' it to be so in that this factor shows the correct causal behavior. Sadly, this scheme is used as evidence for Hp to be thé cause while thereby 'clearing out' psychosomatic causation. Most probably, with other research one could *within the same scheme and equally well* conclude the psyche to be thé cause, 'clearing out' Hp. We need to look further than that, as intended in the remainder of this article. The result is certainly messier, but that cannot be a reason to relinquish our efforts.

Most importantly, there is a huge difference between case (1), being how causality is more or less conceived in many cases of medical causation, and case (7), depicting

reality. Needless to say that this is highly problematic in the medical domain, especially when a whole subdomain (such as psychosomatics) is being diminished by this. In the remainder of this article, we will try to understand the causes of this dire situation. Beside our diagnostic efforts, we also point to and propose some elements of a therapy, though the patient will probably never get cured completely.

Cause is in the eye of the beholder

To many who are not acquainted with thinking about causality, it may come as a surprise that human beings actually have *invented* causality. We have not discovered it – as a principle – in any way. In reality, causes do not exist. We do not 'see causes', as we also do not 'see colors'. Of course, light waves and frequencies exist. A color however is a subjective experience. There is no color in the objective world. Colors are *qualia*: things that only exist in perception, therefore not outside of a perceiver. They emerge from our relationship with reality. Of course, colors and causes are important. We enjoy the former and better take care of the latter. Yet like color, causality is not a natural kind phenomenon. Causal connections are, as according to David Hume, the products of our observations [3].

A metaphor may say more than a million words. Say we are looking at shadows on a wall seeing them collide. Yet shadows cannot collide. There is no intrinsic causality between the movement of one shadow and that of another. Now we turn around to look at the things that form the former shadows. Yet these are like 'shadows' in their own right. No causality except in our own subjective experience that we already had when looking at the shadows on the wall and that we are just not able to surpass. When do we need to surpass it? We can speak about causes anyway, as we will do in the remainder of this article. Meanwhile, it is worthwhile and humbling to acknowledge that causes do not *objectively* exist. Otherwise said: if we would take everything out of reality except causality, nothing would be left. We may remember in this Bertrand Russell's 1912 assertion that the word 'cause' may in the end be so "inextricably bound up with misleading associations" as to make its extrusion from the scientific vocabulary desirable [4, p.340]. This leaves us pondering over the fact that in the end, causality itself is also a subjective choice. We choose to act as if it exists since it is useful for us to do so. Let's continue doing so in the remainder of this article while being aware that in a perhaps more than only philosophical way we are not on solid ground.

Statistical correlations and causes

Correlations are actions that are linked to each other, regularly happening either at the same time or one after another. A ubiquitous difficulty for medical scientific progress is the existence of 'confounding factors' in this: one correlational element seems to be the 'cause' of another while just being another consequence of a mutual cause. Schematically:

A => ↓B AND ↓C ['↓' means: 'diminishment of']

may look like

A => ↓B => ↓C [or A => ↓C => ↓B]

For example: A = antibiotic, B = Hp and C = peptic ulcer.

Correlations never prove direct causalities. For instance, theoretically, in the example of the previous line, the placebo-effect may be an explanation. It might for instance change the local blood flow which in turn might make life more difficult for Hp. At the same time, through still other pathways, it might help in getting the ulcer cured. The scheme then becomes:

'Taking of A' => placebo effect / change in local blood flow => ↓B AND ↓C

As far as we know, this possibility has not been investigated yet. We also do not think it to be the case. Yet further on in this article we will re-encounter the placebo effect in different, rather surprising ways.

Medical scientists constantly strive to avoid confounders. The Popperian process of falsification can be seen as a search for confounding factors/situations. These confounding factors of course have causality in their own right. Finding confounders equals finding causal factors. Sometimes, in serendipity, these causal factors are themselves worthwhile to further investigate. Moreover, especially in medicine, correlations are always messy, as is nicely worded by [5] as "All statistical modeling is a compromise between inconvenient truth and useful fiction." Indeed as these authors say: "There is probably no real exposure-disease relation with an exactly logistic form, or with time-dependent hazards that are exactly proportional." [5]

While most correlations are not causes, a cause – taking into account the above said – is one special type of correlation. On the other hand, causality is always involved in correlation in that truly correlating elements (pure chance being kept out of the

picture) must have a mutual cause. That is also the case if one causes the other, in a causal chain. In this sense causation has been called by Pearson the 'limit of correlation' [3, p. 409]. However, correlations are statistical while causes are in principle not. Therefore, "statistical methods cannot establish proof of a causal relationship in an association. The causal significance of the association is a matter of judgment which goes beyond any statement of statistical probability." [6, p. 20] No observational study provides data that definitely warrant causal claims. The way we look at causes as limits of correlation is finally an element of confusion, the promotion of a correlation into a cause being always a leap. Where the psyche is involved, for several reasons this leap becomes huge. One of the reasons lies in the dualistic question: how can something that is immaterial influence (= cause a change of) something material and vice versa? The answer is straightforward and – again – related to causality itself, namely that there is no influence since they are the same thing. Psyche and body are like art and paint: two views upon the same painting. The art is not in any way the result of the paint. The way we mostly handle causality itself is at the core of this 'problem'.

Causal criteria

In an effort to unequivocally determine whether cigarette smoking is or is not causing cancer, the Surgeon General's Advisory Committee (1964) explicitly used five pre-stated criteria for causal inference [6][7]. Later on, these have been adjoined with a few more by Austin Bradford Hill, forming together the 'Hill criteria' for drawing causal conclusions [8]. Their basic outline has evolved little since then. Hill's 9 criteria are: ***1) strength of association*** (not equivalent to statistical analysis in which the use of a big population while showing weak association may lead to statistically significant results. It is expressed as 'relative risk' or 'odds ratio'); ***2) consistency*** (identity of findings in repeated studies preferably carried out by different researchers, in different places and times. Irreproducibility has the significance of falsification); ***3) specificity*** (degree of regularity with which the occurrence of a causal factor is connected with the occurrence of consequence); ***4) temporality***; ***5) biological gradient*** (overlapping with next two); ***6) plausibility***; ***7) coherence*** (measure of consistency with current biological knowledge); ***8) experimental evidence*** (most valuable is the demonstration that the effect will not come if the presumed cause is removed) and ***9) analogy*** (e.g. what happens in animals may happen in humans, same cause for similar diseases) [9].

These are not, according to Hill himself, “hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. There are ambiguities, fallacies and vagaries associated with each criterion. None of them can bring indisputable evidence for or against the cause-and-effect hypothesis.” [10] They are useful to make up our mind about whether there is any other way of equally or more likely explaining the facts. Moreover, causal criteria as described in textbooks can have variable interpretations and applications in practice, often excluding or even altering criteria without giving reasons. Such lack of transparency of methods undermines the purpose of the causal criteria to promote objective, evidence-based decision making [6]. Even idealized causal criteria have fatal flaws undermining their use [4].

Later on, Susser described 5 strategies for coming to judgments about causality: using causal criteria, simplifying the conditions observation in study design and execution, screening for confounders analytically, elaborating associations analytically and using significance tests and power analyses to address the role of chance [7, p.109]. Susser explicitly stated that judgments about causality “are reached by weighing the available evidence; there are no absolute rules, and different workers often come to conflicting conclusions.”

[11, p.140-1) In addition to this, causal inferences that make use of causal criteria are neither deductive nor inductive, yet have an important role to play in ‘inference to the best explanation’ [12]. Even so they have many problems but as such, causal criteria, exemplified by what A.B. Hill referred to as ‘aspects of (statistical) associations’, have pragmatic value as tools for people interested in making causal claims for preliminary assessments of statistical associations.

Causal criteria show us that contrary to a large part of medical scientific on-the-field opinion, RCTs and meta-analyses are by themselves *not* the best Gold standard to deduce causality. This is: they are not enough but merely (an indispensable) part of a whole that needs to be taken into account to arrive at the Gold standard of causality. Experimentalism and rationalism really do need each other.

We see the causes that interest us

The past has been cause of the present. When something is ‘the cause’, it is already something of the past. The present is never ‘cause’. Likewise, the present can have a goal or purpose but not be the cause of that goal. Maybe something unexpectedly happens, then the goal doesn’t happen in the future. Then there will in that future

not have been a cause in this present. Which means it isn't here at this moment. So in fact nor cause nor goal exist in the present. Yet something can *have* a goal, just as it can *have* a cause. Causes and goals are tools of communication, as said, elements not of the perceived but of the perception.

This way, when someone shoots another person, is the bullet the cause? Actually the question is: "do we find it worthwhile/interesting to look at the bullet as cause"? If not, we may better call it 'risk factor' or in special circumstances 'necessary factor' (NF) just as the gun from which the bullet comes, the mine that the bullet's metal has been extracted from, the metal-making star that exploded a billion years ago, the person who educated the person who pulls the trigger, etc. There is a whole 'space of NFs' for this very concrete action to take place. The point is that we don't care so much for most of these factors. We are concerned with what works. We confine the 'space of NFs' (SNF) for pragmatic purposes to what we pragmatically need. That is as said, a strength and a weakness. It makes us especially weak if we take for granted the reason(s) why we make this or that specific confinement. Looking at HP for instance, we may see in it an NF for PUD, at least in several distinct causal patterns. In these patterns, the concept of HP infection has a causal relationship with the concept of PUD. That makes it a useful mental tool. HP as thé cause of PUD however is a choice, not a discovered fact. We can then ask ourselves for which pragmatic reasons we should make this choice and for which maybe another one.

Here we come to the general 'need for causality' itself. At first sight, it is to understand and control. That is straightforward and useful. Causality this way has brought us technology for instance. Knowledge is power. Yet there is of course an essential difference between understanding and controlling and the *perception* of understanding and controlling. More often than not, we see that perception takes precedence over the real thing. Apparently, we need the perception of control more than we need control itself. Even more, the relative lack of perception of control is according to many investigators on that field the very basis of 'distress'. We want to 'feel in control' even if we undeniably and also knowingly do not have control. Knowing part of the future through causal reasoning for instance, even when this future is uncontrollable, gives us this feeling. Viewed this way, causality is basically about the perception of 'knowing – or thinking to know – the future' at least a bit more: "when (I do) X, then Y will happen". In concrete medical practice, one of the reasons to choose for a specific cause can also simply be that the chosen cause has

an easy cure while another may not. Causality makes us feel secure: “we are in control”. However, in one specific circumstance this backfires completely into our own face, namely: when confronted with a cause that by itself, in principle, makes us *feel* that we are actually *less* in control then we generally think. Such is the predicament of ‘psychosomatic causes’: they show us that in a domain as important as health apparently we are definitely *not* in absolute control within our own mind… Because: why would one choose to become ill? Even more: why would one make oneself ill even while at the same time having no idea as to what causes oneself to make oneself ill? These questions are mind-boggling and something we are almost naturally inclined to avoid.

We generally like to see causes in actions of specific, concrete things. For instance we see gravity as the pulling of the earth. The apple falls. In reality, it may as well be a ‘pushing’ from emptiness outside the earth since there is less emptiness in the center of the earth than out in space. Actually, this might also parsimoniously explain intra-nuclear force and the ever more rapid expansion of the universe. But it is harder to conceive because we like to see causes in concreteness, in the first place in ourselves as agents of free will, ‘intentionality’. We let our sense of causation be guided by how we like to see ourselves. That may not always be the best option.

Until now, we have concentrated upon the general picture. As regarding the cause in any *specific* situation, one can look at case (1) in three different ways: 1) there is only one cause, 2) there is only one cause worth consideration and 3) there is only one possible cause. Of these three, physician as well as patient mostly look at this in practice as implicitly option 3). This is: there may be many possible causes for a generic situation, but in any specific instance (any specific situation), the search is for thé cause even when one is not aware of doing so. It seems like searching for thé cause is ingrained in human thinking. The evolutionary strength of this in most non-complex circumstances lies in decisiveness. A weakness lies in the non-completeness and the probability to go astray in complex circumstances such as where human psyche and body coalesce into psychosomatic disease.

If only concepts may be causes, psyche may not

In psychosomatics much is not readily prone to operationalization without losing the essence. This poses serious difficulties *because* operationalization has been put at

the center of medical science. The latter is a choice for one specific view upon reality. In combination with a generally bad state of causal thinking, the road towards materialism and loss of 'human depth' in medicine lies open. The idea of Hp being thé cause of peptic ulcers while the psyche having little or nothing to do with it, is an example.

Looking for conceptual causes leaves out the subconceptual domain. Yet a lot of research points to the fact that even our so-called conscious decisions, the 'causes' of what we see as our conscious actions, themselves originate in non-conscious, subconceptual processing. Neuroimaging techniques are increasingly showing this 'the hard way' [13][14][15]. In order to have a clear view upon causality in psychosomatics, we need to acknowledge that we are beings with a lot of non-conscious, subconceptual awareness and decision taking. This has serious consequences upon our sense of free will, which to many may be a heavy burden. If the body is cause of illness, one is not responsible; if a biochemical imbalance in the brain exists -> not responsible. In fact, only *conscious* 'free will' is deemed to be an entity of responsibility. In other words, the 'responsible I' is locked in consciousness. That is right if 'I' am my consciousness and my body is not deemed to be 'I'. Or even worse: "It's not me, it's my brain, or my dopaminergic system of gratification, that caused my behavior." Or something outside me altogether. If it's not 'I', then many people *need it to be* something outside the own mind altogether… or the sense of 'free will' is jeopardized.

The concept of causation historically stands in relation to free will. Contrasting to things that 'just happen', in ancient times only gods, people and to a lesser degree also animals were deemed to cause things to happen. Things could not cause other things to happen. The latter just happened, in a natural flow. Needless to say that in such a world, seeing things *within* human beings as causative was difficult. Mind could not be a material thing. It could not be the brain. At present, there is a dual relationship with this idea. Is it me *or* is it my brain? We should be careful with our causational deductions. Nowadays, male individuals commit 90% of all murders worldwide, mostly at an age when testosterone levels are highest. Is testosterone therefore part of the causational pattern? Should one thus judge a female murderer harder than a male one? That doesn't seem right. As another example, there is a tendency to look at the environment as cause of the problem of obesity since people are genetically not much different from several 1000 years ago. However, that they did not overeat then as they do now in an age of full supermarkets does not make

the latter ones thé cause of obesity, nor does it make people less responsible in the end. This (mis)use of causation stands in opposition to respect of 'free will' of total persons. This is a very ethical issue. One should not make obese people 'guilty', but at the same time give them all means and support possible for due responsibility. This is not done by making the environment into the culprit. The difference between guilt and responsibility is very much related to the question 'who' causes what and how/why. Without taking into account the subconceptual level of human mental processing, this question gets no decent answer.

Without such answer, the result is at present a kind of flip-flop between 'being the cause or not' of the own behavior. In appearing to be the cause of own 'bad behavior' – for instance being the cause of one's own illness – people tend to be quickly entangled in feelings of guilt. This makes them want to NOT be the cause of own 'bad behavior'. More and more we see conceptual diagnoses being (mis)used in this landscape. By making causes concrete and alien, an individual's possible 'guilt' is relieved, but also his responsibility is diminished.

Diagnosis: the naming of the cause?

Intrinsically, diseases are themselves not causes of symptoms, therefore the diagnostic process is essentially not about looking for causes but for explanations, patterns of which one or more symptoms can be elements. One can then look for possible 'causes' of these patterns. This is especially so in psychiatry and psychosomatics (functional syndromes). But even a flu does not cause fever. The fever is itself part of the flue. Here one can see the infestation by viruses as cause, leading to an immune reaction and discernible symptoms. In psychosomatics on the other hand, causes are not as identifiable as simple viruses. Psychosomatic causality is much fuzzier, with NFs in general not easily identifiable. A search for 'the cause' in order to alleviate the need to *consciously feel in control* is not a scientific attitude. For instance: ADHD was from start on not defined as a disease but as a conglomerate of symptoms put together by convention, 'conceptualized' but not 'discovered'. Yet people, including caregivers, worked from very early on with the diagnosis of ADHD as an explanatory entity, even more, as a *cause* of symptoms. This is clearly a misuse of diagnosis. There are many more examples. An important goal of such diagnoses is a direct, concept-based feeling of control. As in many such cases, the cost to patients as well as to society is extremely high.

In physics (as in purely physical diseases if they exist) we have successful laws for the job of discerning causality. In psychosomatics, the picture is very different. There are no mathematically strict laws. Moreover, how does conscious 'I'-control stand in relation to a more complete-person control? The alternative is seeing a psychosomatic diagnosis as a mere description of a present situation, a set of correlations without direct 'causal' implication of any of these correlations. Thinking this way makes a person less vulnerable to conceptual traps. E.g. someone wants to quit smoking. His nicotine addiction *has* a causal pattern with smoking in the past as an element. The causal pattern itself is vast, with lots of kinds of elements. He also *has* a goal pattern, of which *quitting smoking* is an element. Feeling good while quitting and having quit smoking is probably another, even more important element. At present, the person *has* these elements. They are part of his present pattern. It is in this that he can be supported. Causes and goals are not facts within his present pattern. They are elements that can be interpreted to a huge degree. One can only change in the present. Moreover, focusing on past causes as hard facts makes a patient weaker and 'guilty'. This makes the processing of causality an important and ethical factor in coaching / therapy. Central to this is a choice between a conceptual feeling of control versus a much broader 'fully human control' that comes together with a messier reality in which close personal contact becomes more prominent. Indeed, this is then a central part of what 'healing' is about. The non-specific factor *empathy*, proven to be so important in healthcare relationships, gets central stage. This way, causality leads us to the core of what it means to be fully human, *especially* in the domain of psychosomatics.

So is Helicobacter pylori thé cause of PUD?

There is a high prevalence of Hp, two-thirds of the world's population being affected, yet most remain asymptomatic [16][17]. In some less developed countries, less than 1% of the population suffer from PUD while Hp prevalence is more than 70% [18]. Moreover, epidemiologically seen there is no good correlation at all between DU and Hp prevalence [2]. People who develop PUD do so mostly after decades of Hp infestation [19].

In addition to this, there is a notorious dichotomy between the presence of active peptic ulcer crater and symptoms of PUD, mainly dyspepsia. The diagnosis of 'functional dyspepsia' is made by exclusion of an ulcer crater or any other organic cause. This means that in case of ulcer-dyspepsia, the difference with functional dyspepsia lies in the presence of the ulcer. It is not straightforwardly clear therefore in the specific ulcer-dyspeptic patient to what degree the dyspepsia is caused by the ulcer or by a concomitant 'functional' part. Moreover, up to 40% of patients with a healed ulcer crater continue to have some degree of dyspepsia [20]. So while it is proven that Hp is causally involved in peptic ulcer craters and that these are causally involved in dyspepsia, both involvements are far from simply straightforward. The high percentages of 'cure through antibiotics' are found mainly when investigators rather myopically look at the ulcer instead of at the complete picture. At the other side, it is clinically known for centuries that psychosocial factors play a major role in the etiology of dyspepsia. This and direct influences of the psyche on peptic ulcers themselves are receiving additional strong proof till this date [21][22][23][24][25][26][27][28][29].

The idea of the bacterium in the stomach as cause of peptic ulcers has been welcomed by many in a way that makes one think of a not-so-hidden agenda to oust out the psyche from this domain. History shows a pendulum motion in this regard. Peptic ulcer was also the first exemplar of psychosomatic disease as such investigated and famously published about in 1934 (Psychoanalytic quarterly) by one of the 'fathers of psychosomatics', Franz Alexander [30]. The present rather myopic view on bacterium and ulcer, as well as the former rather myopic view on psyche and ulcer, makes one think about how 'causality' can be misused in the domain of psychosomatics and even more generally in the whole domain of medicine for the sake of researchers' (and industry's?) interests. Instead of just blaming people or institutions, one can see in this an incentive to really very much further the cause of 'good causal thinking in medicine'. This is of such primordial importance that it may strike one as very weird to see how little effort is invested in this domain…

In the Middle Ages, it was thought that a kind of snake could live in the stomach as 'cause' of gastric symptoms. People used remedies to 'kill the snake'. There was definitely an appeal of such causal explanation. The 'beast in the stomach' hypothesis came back immediately when at the beginning of the 20th century Virchow made fashionable the idea of bacteria causing illness. However, no bacteria

were found in the stomach so it was thought that the high acid levels made this impossible… until another story began in Australia a few decades ago. The extreme focus by many on Hp as thé cause of PUD at the detriment of psychological factors is thus not without historical background. Once and for all, it may be time now for a much more integrated picture.

A Good Cause: Future of Causal Thinking in Medicine

The last decades and especially since 2000, medicine has taken the road of 'evidence based medicine' (EBM) whereby the evidence is mainly / almost exclusively sought in experimental evidence while devaluing theoretical models [31]. In this, modern medicine as developed from around the beginning of the nineteenth century stands in stark contrast with disciplines like biology, chemistry and physics in which modeling and experimentation have always been much closer intertwined. While modern medicine has been modeled upon physics at its start (hence also the term 'physician'), it has clearly taken a different road since. A main reason is that medicine operates in a much more open world, in which modeling is always tricky – but so is experimentation – as well as directly having huge implications upon human suffering. It seems like it is too much to take explicit responsibility for a model that may always be wrong in the end, like the previous millennia old 'model of four humors'.

Yet there is a largely implicit model behind the whole of present-day medicine. Unfortunately, this is a very mechanistic model based on 'hard dualism' in which psyche is devalued from having much direct influence upon somatic disease, at the same time being liberated from (the idea of being responsible for) it. The patient receives this liberation from the transaction but at a huge cost and without actually having a really good choice within the domain of regular medicine. The physician gets a huge status from this same transaction, at the cost of a *hell* of a lot of work and of 'being scientific while actually not being scientific' in the burgeoning domain of psychosomatics'. Present medical causal thinking is the glue that fixes the situation. The dire state of medical causal thinking is of course not consciously sought. Yet vested interests in a status-quo are enormous.

Theories are important as fundamental elements of the epistemological underpinnings of modern science in general. Theories integrate otherwise disparate knowledge, enhancing in-depth explanations and predictions and allowing the generation of new knowledge by exploring a theory's conceptual and dynamic implications [31]. As this author points out (p. 270): "… moving RCTs into a framework where the essential connection was evidence to belief and not events to events would refocus the purpose and methods to exactly where I will argue they should be: the relationship between theory and evidence. That would not be a pleasing outcome for the EBM hierarchy of evidence because a robust, and therefore explanatory, theory would become the Gold standard, not RCTs."

As experimental evidence even in the best case only works well in a closed world, Nancy Cartwright is right in saying that "In an RCT, if we are lucky, we find the average difference in effect produced by the treatment in the population sampled. That does not tell us what the overall outcome on this effect in question would be from introducing the treatment in some particular way in some uncontrolled situation, even if we consider introducing it only in the very population sampled. For that we need a causal model." [32, p.238] Moreover, the blindness of many double-blind RCTs has been severely criticized [33]. As to meta-analysis, "it has a real but limited role in causal inference, adding to an understanding of some causal criteria. Meta-analysis may also point to sources of confounding or bias in its assessment of heterogeneity. … Meta-analysis provides a more formal statistical approach to the criterion of consistency as well as a way to identify heterogeneous groups of studies." [34]

In short, scientific theories are essential to attaining really scientific causal knowledge, in medicine as well as in any other science. In trying to get rid of this requirement, causal thinking in scientific medicine has maneuvered itself into what very much looks like a dead-end street, resulting in huge and growing costs as well as huge clinical disappointments that are more and more showing, especially in psychosomatic domains such as the larger area of chronic functional pain syndromes. The proposed solution is at present again and again 'more of the same'. In view of the dire state of medical causal thinking, this solution may according to us be part of the problem itself.

Conclusion

Medical causal thinking is at the basis of any medical clinical action as well as medical scientific progress in general. Yet it is at present in a dire state. Especially in the psychosomatic domain, this leads to disasters for many patients as well as a tremendous cost for society. Looking at Hp as 'the cause' of PUD at the detriment of any psychosocial factor involved is an example. This way problems grow bigger and bigger, as we can see in ever more psychosomatic suffering of all kinds. This can only stop if we as healthcare providers dare to look at ourselves very critically and become also in a deep way personally involved. Scientific medicine evolving from this will become more humanistic with a keen eye for deeper layers of human beings as well as 'being human'. The issue is theoretical, pragmatic and extremely ethical. Pointing this out does not swiftly change the situation. A lot of vested interests, including those of patients themselves in their conscious 'I' faculty, lead to inaction. What lies ahead first and foremost is good and clear theorizing, followed by taking and supporting the necessary responsibility in order to make ourselves, as causes of what we are continuously constructing in this world, more deeply human.

References

[1] accessed at http://nobelprize.org/nobel_prizes/medicine/laureates/2005/press.html

[2] Hobsley M, Tovey FI, Holton J. Precise role of H pylori in duodenal ulceration World J Gastroenterol 12 (2006), pp. 6413-9.

[3] Pearl J. Causality – Models, Reasoning and Inference. New York: Cambridge University Press, 2009:464

[4] Ward A. Causal criteria and the problem of complex causation. Med Health Care Philos. 2009 Aug;12(3):333-43. Epub 2009 Feb 14.

[5] Kaufman JS, Cooper RS. Seeking causal explanations in social epidemiology. Am J Epidemiol. 1999 Jul 15;150(2):113-20.

[6] Parascandola M, Weed DL, Dasgupta A. Two Surgeon General's reports on smoking and cancer: a historical investigation of the practice of causal inference. Emerg Themes Epidemiol. 2006 Jan 10;3:1.

[7] Kaufman JS, Poole C. Looking back on "causal thinking in the health sciences". Annu Rev Public Health. 2000;21:101-19.

[8] Vonka V. Causality in medicine: the case of tumours and viruses. Philos Trans R Soc Lond B Biol Sci. 2000 Dec 29;355(1404):1831-41.

[9] Carneiro AV. Causal relationships in medicine. Rev Port Cardiol. 2005 Mar;24(3):443-9.

[10] Rothman, KJ, and Greenland S. Causation and causal inference in epidemiology American Journal of Public Health 2005;95 (S1): S144–S150.

[11] Susser M. Causal Thinking in the Health Sciences: Concepts and Strategies of Epidemiology. New York: Oxford Univ. Press, 1973:181

[12] Ward AC. The role of causal criteria in causal inferences: Bradford Hill's "aspects of association". Epidemiol Perspect Innov. 2009 Jun 17;6:2.

[13] Bode S, He AH, Soon CS, Trampel R, Turner R, Haynes JD. Tracking the unconscious generation of free decisions using ultra-high field fMRI. PLoS One. 2011;6(6):e21612

[14] Soon CS, Brass M, Heinze HJ, Haynes JD. Unconscious determinants of free decisions in the human brain. Nat Neurosci. 2008 May;11(5):543-5.

[15] Haynes JD, Rees G. Predicting the stream of consciousness from activity in human visual cortex. Curr Biol. 2005 Jul 26;15(14):1301-7.

[16] Melmed RN, Y Gelpin Y. Duodenal ulcer: the helicobacterization of a psychosomatic disease? Isr J Med Sci 32 (1996), pp. 211-6.

[17] Atherton JC The pathogenesis of Helicobacter pylori-induced gastro-duodenal diseases. Annu Rev Pathol. 2006;1:63-96.

[18] Ballesteros-Amozurrutia MA Peptic ulcer and Helicobacter pyrlori. Results and consequences of its eradication Rev Gastroenterol Mex 65 (2000), pp. 41-9.

[19] Cover TL, Blaser MJ. Helicobacter pylori in health and disease. Gastroenterology. 2009 May;136(6):1863-73. Epub 2009 May 7.

[20] Soll AH. Peptic ulcer and its complications. In: Feldman M, Scharschmidt BF, Sleisinger MH, editors. Sleisenger and Fordtran's gastrointestinal and liver disease Pathophysiology/Diagnosis/Management. Philadelphia (Pa)7 WB Saunders, 1998. pp. 620– 78.

[21] Räihä I, Kemppainen H, Kaprio J, Koskenvuo M, Sourander L. Lifestyle, stress, and genes in peptic ulcer disease: a nationwide twin cohort study Arch Intern Med, 158 (1998), pp. :698-704.

[22] Lam SK, Hui WM, Shiu LP, Ng MM Society stress and peptic ulcer perforation J Gastroenterol Hepatol 10 (1995), pp. 570-6.

[23] Levenstein S, Kaplan GA, Smith M. Sociodemographic characteristics, life stressors, and peptic ulcer. A prospective study J Clin Gastroenterol 21 (1995), pp. 185-92.

[24] Levenstein S. The very model of a modern etiology: a biopsychosocial view of peptic ulcer Psychosomatic Medicine 62 (2000), pp. 176-185.

[25] Levenstein S. Psychosocial factors in peptic ulcer and inflammatory bowel disease J Consult Clin Psychol 70 (2002), pp. 739-50.

[26] Magni G, Di Mario F, Aggio L, Borgherini G Psychosomatic factors and peptic ulcer disease Hepatogastroenterology 33 (1986), pp. 131-7.

[27] Piper DW, Tennant C. Stress and personality in patients with chronic peptic ulcer J Clin Gastroenterol, 16 (1993), pp. 211-4.

[28] Ol'khov OG, Pertseva TA, Gerasimchuk ON, Khrustaleva OS, Sokolovskiĭ AV, Baĭbuz TE. The assessment of the psychophysiological status of patients with duodenal peptic ulcer Lik Sprava. 3-4 (1996), pp. 120-2.

[29] Tsimmerman YS, Tsimmerman IY. Depressive syndrome in gastroenterology: diagnosis and treatment Klin Med (Mosk) 85 (2007), pp. 15-23.

[30] http://www.psychosomaticmedicine.org/content/26/3/203.full.pdf+htmlIN MEMORIAM Franz Alexander, M.D.

[31] Thompson RP. Causality, mathematical models and statistical association: dismantling evidence-based medicine. J Eval Clin Pract. 2010 Apr;16(2):267-75.

[32] Cartwright N. (2007) Hunting Causes and Using Them. Cambridge: Cambridge University Press.

[33] Park J, Bang H, Cañette I. Blinding in clinical trials, time to do it better Complement Ther Med. 2008 Jun;16(3): 121-3.

[34] Weed DL. Interpreting epidemiological evidence: how meta-analysis and causal inference methods are related. Int J Epidemiol. 2000 Jun;29(3):387-90.

Serial Treatment Assumption Testing (STAT) Towards Better Evidence for Evidence Based Medicine

This article exposes the lack of control of 'blindness' in double-blind studies, and raises the potentially substantial gap between theory and practice in this regard. It also examines what could be done to remedy this situation, taking into account both conscious and unconscious processing. Science should be subordinate to reality, rather than reality – or a semblance of it – being subordinate to science. Within the domain of conceptual thought, we therefore need a level of rigor that far surpasses that which currently exists.

4.11 FULL ARTICLE: Serial Treatment Assumption Testing (STAT) Towards Better Evidence for Evidence Based Medicine

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Submitted in: "Trials"

Abstract

Background

Double-blind RCTs are the mainstay of evidence based medicine to such a degree that many have the impression that they have been with us for a very long time. Yet it was only in the 1970s that they became regularly used in the US. They became mandatory for FDA approval of new medications around 1980. The basic question remains: are double-blind studies really blind?

Methods

A literature overview shows that little is known about degree of blindness. Moreover, what is known points to a suboptimal situation. The main reason may be found in the core itself of double-blind studies: the still not well-understood placebo-effect. Specifically: can we best look at the placebo-effect as a conceptual or as a mostly subconceptual phenomenon? May the intended effects and side-effects of treatment, including those that one is not consciously aware of, be substantially 'placebo enhancing'?

Results & Conclusions

We bring to bear subconceptual processing insights from the field of Cognitive Neuroscience, together with pragmatic implications in order to explain the high degree of non-blindness of double-blind RCTs. Contrary to the present inclination towards relaxing the double-blind procedure, it may need to be made even more stringent. We posit *serial treatment assumption testing (STAT)*, an original concept worked out in this article, as a tool for this. RCTs with no reports about levels and assessment modalities of treatment assumption should from now on arguably be regarded as not evidence based.

Keywords: treatment assumption; double-blind RCT; placebo; autosuggestion; cognitive neuroscience; STAT

Background: 'At face value' is not enough in medicine

Many 'innovative' procedures that at first were accepted by the medical community (e.g. glomectomy for bronchial asthma, levamisole for HSV…) have subsequently been found ineffective. Yet at the time, peer-reviewed uncontrolled case studies found beneficial effects, according to a later meta-analysis of 5 such procedures, in 70% of patients. [1] More recently, a meta-analysis of 16 observational cohort studies showed a relative risk for coronary artery disease among women taking estrogen, of 0.5. A double-blind RCT however on 2763 women showed no reduction of this risk. [2] An RCT on 16.608 women even demonstrated an increase in coronary artery disease. [3] Yet another example: in the years before 2002, 650.000 arthroscopic operations with debridement and lavage were performed yearly on the osteoarthrotic knee in the US, with a cost of $5000 each. Noteworthy, countless retrospective 'case series' showed a substantial pain relief. Then however an RCT was performed (N=180) with sham surgery (skin incision only) used as placebo versus the real operation, showing no difference in pain or functionality over 24 months postoperatively. [4] Examples such as this show the importance of optimally conducted RCTs. Although part of the explanation may be a reporting bias, the last example also shows, among many other studies, the power of placebo.

The more double-blind a study, the less a treatment's efficacy according to that study tends to become. [5][6][7][8] E.g. Wood et al. found in an overview of empirical studies in meta-analyses the beneficial effects on subjective outcomes being 25% lower in trials labeled 'double-blind' versus not. [9] Oesterle et al. found in trials of laser-treatment for angina using blinded and unblinded outcome assessors an exaggeration of the effect by 69% (29-87%). [10] Clearly 'at face value' is not enough. We need blindness in order to see more objectively. [Note that in this article, we do not elaborate upon the concept 'double-blind'. A good overview is given in [11].]

The state of double-blind

In a survey of 200 RCTs in top journals, 50% of the authors who used the term 'double-blind' did not make any statement about who was blinded. In another 35% they specified only one group. [12] In five top journals (+/- 2000), Montori et al. found an explicit reporting of blinding status (who got blinded) in less than 25% of 40 RCTs. [13] Shapiro et al. found in a meta-analysis that at the end of RCTs, patients guessed right in 72% of cases (17 published studies), physicians in 83% of cases (14 published studies). For cross-over studies (alternating active treatment and placebo during a few weeks), percentages were respectively 93% and 100%. [14] In a systematic review of 63 randomized placebo controlled trials, according to Park et al. about 73% of studies turned out unblinded. They generally contend that "the optimistic assumption that blinding remains intact as intended throughout the trial proved to be untrue." (2008) [14]

When treatment is compared with active placebo (= with side-effects), the numbers tend to be lower but still substantial. In one double-blind study with amitriptyline/active placebo (benztropine mesylate), correct guesses by patients were 62.5% on amitriptyline, 55% on placebo. Correct guesses by a nurse were 73% - 75%. [15] These authors conclude that "all reports of blinded trials should include data on patient and clinician guesses as to patient assigned condition." The lack of such information may be due to concerns about trial invalidation. [16] Turner et al. strongly recommend against dismissals in such cases since most trials may be more or less tainted by unblinding. [17]

However, reporting upon (lack of) success of blinding is not common. Even researchers who claim their trial to be double-blind mostly do not report upon their testing of such [18]. Hrobjartsson et al. found evidence on success of blinding, by testing and/or explicit methods of blinding, reported by only 31 of 1599 medical RCTs (2%) [19]. Fergusson et al. examined trials from 5 top general medicine (97 trials) and 4 top psychiatry (94 trials) journals. In 15 cases, the authors provided either qualitative or quantitative evidence on the success of blinding (= 8%), most of them reporting that the success of blinding was imperfect. Only 2 provided a quantitative data analysis of successful blinding. The authors conclude with: "Unfortunately, when we examined the data and analysis provided by these two trials we found that their claim of success is debatable." [20]

So while there is little evidence that blinding is maintained till the end in most trials, the unblinding of RCTs has largely been ignored [14]. Moreover, authors use very

different methods to present blinding-related data if they do so at all. [14] Many authors handle the term 'double-blind' as if this is an obvious term. However, from what degree of blindness should we not call a study 'double-blind' anymore?

Inside the core of double-blind: placebo, power of suggestion

In a laboratory study, IBS patients were tested for pain relief through a placebo when subjected to rectal distention and painful cutaneous heat. The placebo given without further suggestions gave a moderate size effect. The placebo accompanied with positive suggestions doubled the effect size (from 1.6 to 3.0 VAS units), bringing it to the level of active treatment. Noteworthy is also that expectancy and desire for pain relief, both heightening suggestivity, accounted for ± 80% of the variance in visceral pain intensity. [21] A related study with IBS patients undergoing rectal distension by balloon barostat (N=9) after getting placebo versus no placebo showed on fMRI large reductions in brain activation within pain-related regions (thalamus, somatosensory cortices, insula, and ACC). [22]

Suggestion also explains why some placebos work better than others. For instance, for obvious reasons, parenteral administration has a higher suggestivity than oral administration. In a double-blind RCT about antihypertensive effects of ergotoxine, 134 subjects on parenteral/oral ergotoxine versus placebo as agents were followed-up during 143 weeks. Parenteral placebo was dramatically more effective than oral placebo. [23] In a study on 88 highly refractory patients with rheumatoid arthritis (after many types of 'treatment'), subjects received placebo pills during 4 weeks. 50% of the subjects improved. Then normal saline injections were administered, to which 64% of those resistant to placebo tablets responded. Benefits lasted 2 to 20 months. [24] In a study on 44 patients with chronic cervical osteoarthritis, analgesic sham acupuncture was significantly superior to placebo pills. [25]

Kirsch et al. compared a deceptive administration of a placebo in which subjects were led to believe that they really *were* receiving an active drug (caffeine), to a double-blind situation in which subjects were aware that they *might* receive a placebo. The produced effects (on pulse rate, BP, subjective mood) were different, in some instances even opposite. [26] Note in this that the *treatment assumption* – the assumption that one is taking an active product - heightens its placebo-effect.

A related and recent line of research compares open versus hidden administration of medication. 'Hidden' means: concealed to the patient, such as through an intravenous line. In such cases, the treatment assumption (TA) is zero. Colloca et al. compared the analgesic dose needed to reduce pain by 50% with hidden infusions of 4 painkillers versus open infusions. The dose was much higher in cases of hidden infusion. They also compared, in the same situation, the effect of open versus hidden administration of diazepam to patients with high anxiety scores. Anxiety decreased significantly in the open situation, but not in the hidden situation [27]. This might be partly due to a reporting bias, though it is hard to imagine this to be the complete explanation. This research shows that placebo-effects in active treatment groups can be (much) higher than what is calculated by subtracting the effect in the placebo-group from the effect in the active treatment group in double-blind studies generally.

Although some authors remain unconvinced [28], in these and other examples, one sees the power of placebo to be substantial. There are a number of pathways described to 'explain' the placebo-effect, leading us astray in double-blind RCTs if not properly taken into account.

Insights from Cognitive Neuroscience

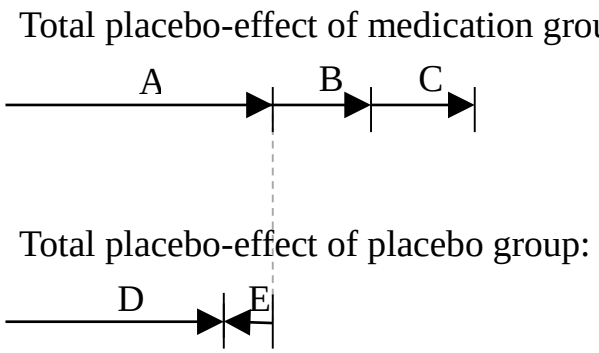
Investigations in Cognitive Neuroscience point to a rich subconscious awareness and decision making [29]. Using fMRI one can trace the outcome of a decision in subconscious brain activity up to 10 seconds before entering conscious awareness. [30][31][32] Vision readily lends itself to direct experiments, while we see likewise phenomena at many levels in mind/brain. E.g. blindsight patients can meaningfully react to information presented to them without their conscious awareness. [29] In a study on normal subjects, 73 pictures of women with differently photoshopped pupil diameters were shown to 27 male subjects. On fMRI, their amygdalae showed higher levels of activity when looking at pictures with bigger pupils while they were not aware of any differences. [33] Another study showed women's preferences for large male pupils to be stronger in the follicular phase of the menstrual cycle than in the non-follicular phase, while not being consciously aware of any difference. [34] In yet another study, pictures of sad faces with different pupil diameters were accordingly judged as more negative and intense, leading in the unaware onlookers to emotionally modulated brain activity. [35]

'Priming' is about the effect of not consciously captured or remembered information on subsequent mental processing. E.g. a word flashed unnoticed on screen can afterwards help to perform correct stem completions. [36] Likewise, in double-blind studies, telling people the effects and side-effects of the treatment, even if they do not consciously remember them, can subconsciously lead towards the right TA. People who previously took related treatments can subconsciously recognize a pattern of effects/side-effects, making them subconsciously aware of which study group they belong to and bringing about a response through priming. This also has implication on double-bind assessment. When forced, they may make the right assumption, while unforced, they say that they just don't know. To the degree that the placebo-effect is due to subconscious processing [37], it is the subconscious assumption that counts.

The full placebo in double-blind studies

We can plot a double-blind situation taking into account conceptual as well as subconceptual sources of placebo-effect. Note that the placebo-effect is not the only source of bias, though we specifically focus on it.

Figure 1*: Total placebo-effect according to its sources, in treatment and placebo group of a double-blind study*



Legend:

A: pure placebo-effect through 'taking the pill'

B: placebo-effect through effect of treatment

C: placebo-effect through side-effects of treatment

E: nocebo-effect through assuming to be in the placebo group

D: A – E

(Note: the length of the lines is arbitrary. They do not indicate relative averages.)

Awareness of effects and side-effects (sometimes even smell, aftertaste…) of treatment heightens placebo-effects also if the person is not *consciously* aware of them. The feeling that "something is happening in my body as a result of treatment" carries the additional suggestion that "I will probably get better," thus intensifying the power of placebo. The total placebo-effect in the treatment group may thereby be quite higher than that in the placebo group. The fact that this substantially works on a subconscious level may explain why neither subjects nor assessors of RCTs generally recognize this. Thereby it can pass unobserved on a big scale.

About E: people who feel, consciously or subconsciously, to not be in the treatment group, may be subjected to negative placebo, the suggestion being "I am not in the treatment group, therefore I will not get better." This way even the spontaneous course of disease may be negatively influenced. Note that E may also heighten on non-pharmacological grounds the difference between placebo and treatment groups in present-day double-blind studies.

Is double-blind evaluation to be relinquished?

One of the CONSORT 2001 recommendations for reporting RCTs in literature (not being guidelines for conducting them) was to report how success of blinding is evaluated. In 2010, CONSORT dropped this recommendation [38] for the following reasons, with for each our objection(s):

- Successful blinding is not related to lack of blinding through identifiable effects or side-effects.

  >< Unblinding through treatment effects is still blindness breach and an argument for Serial Treatment Assumption Testing (STAT).

- If the new treatment is beneficial, presumptions (through positive expectations) would be correct more often than chance guesses, even with totally 'successful' blinding. The test would then be a test on hunches of efficacy. D.L.Sackett therefore recommends to test for blindness before trials, not during them, nor at the end. [39]

  >< This is only relevant for very beneficial treatments. In addition, this should better be countered by neutralizing pre-trial expectations, such as by attenuating overly positive expectations of the treatment being tested.

- People who crack the blind will not acknowledge their 'misdeed' at blindness assessment time.

  >< People tell the truth when asked anonymously and appropriately. Moreover, if the amount of 'crackers' were so high as to make the double-blind-testing useless, then it would also make the double-blind itself useless. This would be improper.

Sackett et al. add to this that blindness testing is not recommended since this encourages subjects to try to 'break the code'. [40] Subjects may then drop out or be non-compliant.

>< The inclination to cheat should specifically be dealt with, such as by explaining why cheating is detrimental, (objectively) controlling wherever feasible, explaining that treatment does not necessarily bring advantages over placebo, asking people's opinion about the new therapy before the trial, ensuring them they will get the therapy for free after the trial and trying to involve people who are less prone to cheat (if this is not confounding). Additionally, one can phrase the questions in a empathic way that minimally arises curiosity or encourages cheating and one can combine these questions with e.g. subjective health-related questions, thereby partly concealing the treatment assumption questions. In view of this, proper TA testing may even heighten commitment of participants, thereby diminishing their desire to cheat.

If blindness cannot be assessed, then the reason(s) why should be stated. Equally so when blindness itself is not possible. The CONSORT 2010 decision seems to be based on the unattainability of the ideal rather than on a pragmatic view. Instead of a

proliferation of blinding assessment procedures, we envision some simple tools enabling the reader of an article – including the possible future meta-analyst – to get a clear view upon blindness to the degree of what is needed and possible. This takes care of the concern that led to the CONSORT 2010 revision, while not abandoning blindness assessment altogether.

Deepening double-blind through Serial Treatment Assumption Testing (STAT)

While CONSORT puts emphasis upon reporting about scientific quality of RCTs [38], our emphasis lies upon reporting of what is interesting to the user of the article. The cause of blindness breach may be a lack of quality or of attainability. At the start of a double-blind study, if allocation concealment is done well, blindness is maximal. At the end of studies, blindness of double-blind studies is in many cases very low. Ideally, we should know at each point how blind the study is. At what point is the 'Gold standard' not golden anymore? This may depend upon the characteristics of each study. In any case, the 'ideal' double-blind study cannot be attained since this would have as placebo a product with the same (side-)effects as the active treatment. That can only be accomplished by using the active treatment itself as placebo, one possibility being that the treatment is totally ineffective. Conversely, the 'ideal' active treatment would be one that would through its effectiveness annihilate double-blindness from start on, making it improvable through double-blind RCTs.

STAT is about asking one question at several occasions during the double-blind study in order to see from which point the double-blind cannot be regarded as really double-blind anymore, taking into account specific trial characteristics and most specifically towards disentangling modulations of TAs through a treatment's effects and side-effects. At least two statistical methods for blindness assessment (James' blinding index and Bang's blinding index) have already been worked out. [41] STAT by itself is not about the specific statistical method as about its pragmatic use as described in this article. According to us, STAT is a small effort in relation to possible benefits. In the following, we describe some ideas about implementation.

A primer to implementation of STAT

The solution space for a practical work-out is constrained through the fact that we cannot simply know whether a TA causes a 'therapeutic' effect or the consciously felt therapeutic effect itself rather causes the TA. As to side-effects in a broad sense, including subliminally felt effects, they too can modulate TA, but it is not straightforward to practically disentangle the modulations of TAs through effects and side-effects. At first sight and as a severe limitation of STAT, they are either both present or not present. However, there are some specific situations that are in reality quite common and in which they are at least more or less separate. We can look at 2 such situations, with 2 ways also in which to expand upon the practical use and usefulness of STAT.

1) If the effect of a treatment is not immediately fully present or apparent to the subject.

   We can then look at the evolution of TAs in a 'STAT-table' with % of right guesses.

Table 1: STAT-table

		t1	t2	t3	…	t_end
patient	**$TA_{placebo}$**	*50*	-	-	-	*e.g. 90*
	$TA_{treatment}$	*50*	-	-	-	*e.g. 75*
care provider	**$TA_{placebo}$**	*50*	-	-	-	*e.g. 95*
	$TA_{treatment}$	*50*	-	-	-	*e.g. 100*

If TAs are high earlier on in the study than the treatment effect, one has to conclude that the treatment effects are not shown as the result of a double-blind study, even if the study started double-blind. It is in such cases not appropriate to call the study results evidence based. The study is a merely observational one. As a matter of fact, neither does this prove that the

treatment doesn't work. The subject might even be 'not consciously aware' of subliminal effects that modulate TAs from early on.

We can further explain this with the use of three extreme cases as to how the effect of treatment and the STAT evolve in time and in relation to each other (see figure 2). In this figure, TA% = % of right assumptions over all groups, above chance, *in function of the highest found TA*. The surface area, being the area between the curves in each figure, might be seen as a measure of a 'STAT-index'. The three cases are:

1. the treatment effect reaches a high level before TAs start being very correct (vertical green line). We thereby know that the treatment effect is not influenced very much by the TA. As to TAs, this is a great study, having a positive STAT-index (e.g. + 60). Most double-blind RCTs at this moment are treated as if they correspond to this.
2. This study has a negative STAT-index (e.g. – 60). Here we see that at the moment that the treatment starts to be effective (vertical green line), most people already make the right TA. Therefore this study is not double-blind. Any conclusions drawn from this study are therefore not evidence based.
3. STAT-index = 0. Note that this figure too is much abstracted. In reality, the lines may be curved in any possible way. The main point is that the effect of treatment and the TAs follow each other.

Figure 2: Three extreme cases as to how the effect of treatment and the STAT evolve in time and in relation to each other

Figure 2 a)

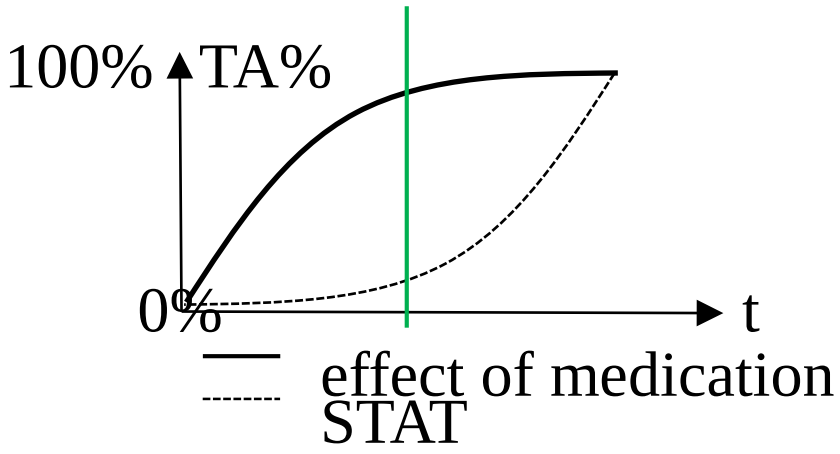


Figure 2 b)

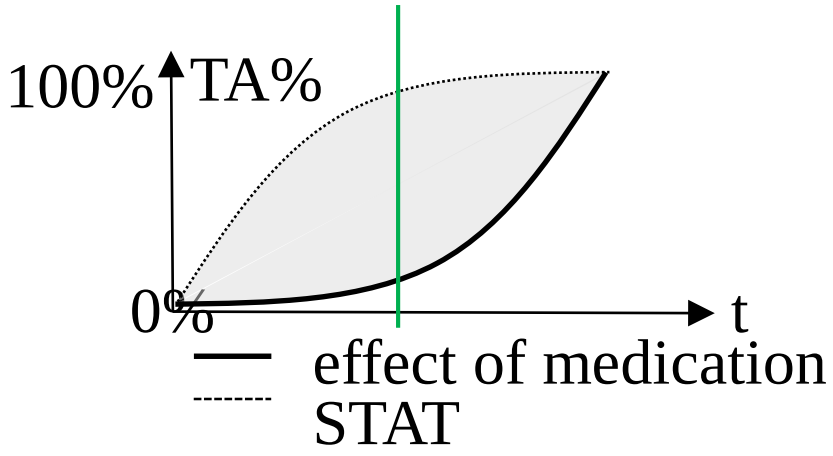
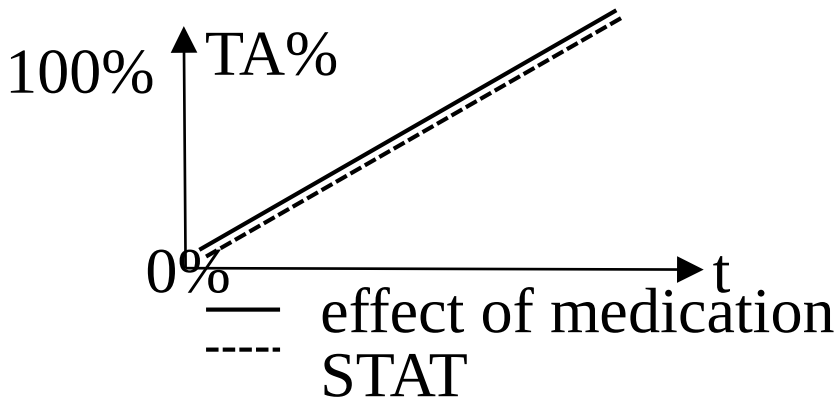


Figure 2 c)



2) If a treatment is not very effective.

In this case, the effects themselves do not modulate TAs very much. If $\mathbf{TA_{treatment}}$ is then relatively effective, we have an additional indication that the studied treatment is not effective by itself. We can put this situation in the following formula according to table 2:

$$(b+d)/(a+c) > (c+d)/(a+b)$$

In plain English: the correlation found between effect and $\mathbf{TA_{treatment}}$ is bigger than the correlation between effect and the treatment itself. This is: $\mathbf{TA_{treatment}}$ has a bigger relative effect than the treatment itself. Thus we are looking more at the effect of the assumption than of the treatment.

Table 2: Treatment groups versus treatment assumption groups

	$\mathbf{TA_{placebo}}$	$\mathbf{TA_{treatment}}$
placebo	*a*	*b*
treatment	*c*	*d*

a, b, c and d are effect sizes

With higher treatment effects, it is not possible to make this deduction.

Note also that this is also relevant when comparing 2 treatments with small differences in effect, especially when they have bigger differences in side-effects.

Studies using active placebos can also take advantage of STAT in that it can be used as an additional indication about whether the active placebo is a well chosen one. The purpose itself of using an active placebo is to bring **$TA_{placebo}$** and **$TA_{treatment}$** closer together. We can directly measure that with STAT.

Finally, we can combine TAs with patient expectations of the treatment's effect. Note the difference between *patient expectations* and *TAs*, which do not incorporate expectations themselves. Before the study, one can make an effort to let expectations be as low as possible. Additionally, one can ask patient expectations before the trial. After the trial, we can look at exclusively those patients with really low expectations. The ideal is that very low expectations make TAs immune to treatment effects. Thus we have a cleaner situation. If the effect then follows the $TA_{treatment}$ rather than the treatment itself, we know we are looking mostly at placebo. Appropriate research has to clear out whether and in which situations this is indeed worthwhile.

About choosing the right TA question

This is important since questions can drive answers. For instance:

- "Do you know to which group you belong – if so, to which?" Some reasons here to say 'no' when it's actually 'yes' are: people understand 'no' as 100%; some have 'cheated' and thereby have a vested interest to say 'no'; people do not consciously know, but unconsciously do.
- "People can sometimes 'feel' through effects and side-effects, even subconsciously, to which group they belong. Please take a few moments, then try to indicate as well as possible to which group you assume to belong." This does not evidently bring out the best guesses. People who try, consciously, may give worse answers than without consciously trying. Conscious effort may *diminish* unconscious processing.

- "Please indicate to which group you *assume* to belong." is probably a good choice of question. This needs to be further explored.

We deem it necessary to make a specific choice. "Don't know" as choice category is not sufficiently revealing since it does not probe unconscious TAs. One can at first pass allow "Don't know" answers, afterwards eliciting forced guesses.

One can eventually ask subjects to explain their assumptions. It is unclear whether this provides reliable information. Since it puts additional burden on the procedure, we do not recommend it except at the last TA of the study.

Further possible advantages of STAT

In case of significant unblinding, investigators should try to find out the reason(s). [41] STAT may at appropriate times, also during the study, indicate the need to do so and provide help in finding out why people leave a double-blind study as well as when and how things can be remedied. In addition, it will make researchers more aware of the problem of unblinding, encouraging them to prevent this. STAT itself may in this respect be suited for specific studies focusing on blinding research and evaluation.

With STAT, we can see where additional proof using an active placebo is indicated. This is according to us the most ethical stance in choosing between a) the certainty to subject a limited number of people to a placebo-with-side-effects under close medical supervision and b) the possibility to subject thousands or even millions to a treatment-that-does-not-work, under much less supervision.

STAT may be directly interesting to pharmaceutical companies, pointing at a sooner stage to whether pilot double-blind RCTs are indeed positive enough to warrant further double-blind studies. As things are, it happens that expensive tests and developments are carried out for quite some time until the company finds out there were flaws from the beginning, eventually leading to higher costs for all stakeholders. Using STAT, the process of medication development as well as FDA approval may become optimized. It can also be specifically interesting in big trials, set up for 'delivering final proof' With much at stake and high study costs, it can be a low-cost addition that heightens the worth of conclusions.

Possible disadvantages of STAT

A possible critique is that blindness is not always possible. We should not demand the impossible before accepting a study as 'good science'. There is a gray zone in which science needs to be rather purely rational than experimentally proven. Insight in placebo heightens skepticism. If a treatment cannot be delivered in a blinded way, that is acceptable but the power of placebo then sharpens Occam's razor. Rationality better be strong or we end up with superstition (again).

A concern may be raised about potentially inviting study participants to suspect the credibility of the treatment overall, which in worst case may jeopardize the entire trial.

"One question at several occasions" can be easy to say but hard to implement properly.

Asking TAs at several times may indeed make subjects curious so that they may make more effort to break the blind. Bang et al. propose, in order to counter this, to ask each subject one TA but at different moments in the course of a study (say one quarter of subjects at each different moment). [42]

Even with STAT, it remains problematic exactly how much unblinding can be tolerated. This also depends on the nature of the study.

STATs of different studies can be difficult to compare due to a number of factors of the studies themselves as well as of how STATs are taken, such as at exactly which moments in the course of a study, with exactly which questions…

Conclusions

Double-blind studies are not optimally double-blind. We build upon insights from Cognitive Neuroscience to explain what may be the main reason for this, namely that the placebo-effect as a modality of primarily subconceptual nature is not properly dealt with. We argue for more consistency and STAT as a practical tool to substantially heighten the quality of double-blind studies for the sake of better and more cost-effective healthcare. RCTs with no reports about levels and assessment modalities of treatment assumption should from now on arguably be regarded as not evidence based. That doesn't mean they are scientifically invalid. However,

regular and any kind of alternative medicine alike should optimally comply to STAT-enhanced EBM using the same insights into the placebo-effect as are valid over the whole range. Arguably, raw STAT-data should be kept for every research in which STAT is possible. True levels of double-blindness, as well as true measures of how much we actually know or even can know about blindness, should be made as open as possible.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

Both authors contributed equally in every aspect of this article. Both authors read and approved the final manuscript.

References

[1] Roberts AH, Kewman DG, Mercier L, Hovell M. **The power of nonspecific effects in healing: implications for psychosocial and biological treatments.** *Clin Psychol Rev* 1993; 13:375–91.

[2] Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. **Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group.** *JAMA*. 1998; 280(7):605-13.

[3] The Women's Health Initiative Investigators. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principle results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002; 288: 321–33.

[4] Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. **A controlled trial of arthroscopic surgery for osteoarthritis of the knee.** *N Engl J Med.* 2002; 347(2): 81-8.

[5] Schulz KF, Chalmers I, Hayes RJ, Altman DG. **Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials.** *J Am Med Assoc* 1995; 273:408–12.

[6] Recurrent Miscarriage Immunotherapy Trialists Group. **Worldwide collaborative observational study and meta-analysis on allogenic leukocyte immunotherapy for recurrent spontaneous abortion.** *Am J Reprod Immunol* 1994; 32:55–72.

[7] Moher D, Ba'Pham, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. **Does the quality of randomized trials affect estimates of intervention efficacy reported in meta-analysis?** *Lancet* 1998; 352:609–13.

[8] Walter SD, Awasthi S, Jeyaseelan L. **Pre-trial evaluation of the potential for unblinding in drug trials: a prototype example.** *Contemp Clin Trials.* 2005; 26(4):459-68.

[9] Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. **Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study.** *BMJ* 2008; 336:601e5.

[10] Oesterle SN, Sanborn TA, Ali N, Resar J, Ramee SR, Heuser R, Dean L, Knopf W, Schofield P, Schaer GL, Reeder G, Masden R, Yeung AC, Burkhoff D. **Percutaneous transmyocardial laser revascularisation for severe angina: the PACIFIC randomised trial. Potential Class Improvement From Intramyocardial Channels.** *Lancet*. 2000; 356(9243):1705-10.

[11] Miller LE, Stewart ME. **The blind leading the blind: use and misuse of blinding in randomized controlled trials.** *Contemp Clin Trials.* 2011; 32(2):240-3.

[12] Devereaux PJ, Manns BJ, Ghali WA, Quan H, Lacchetti C, Montori VM, Bhandari M, Guyatt GH. **Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials.** *JAMA*. 2001; 285(15):2000-3.

[13] Montori VM, Bhandari M, Devereaux PJ, Manns BJ, Ghali WA, Guyatt GH**. In the dark: the reporting of blinding status in randomized controlled trials.** J Clin Epidemiol. 2002; 55(8):787-90.

[14] Park J, Bang H, Cañette I. **Blinding in clinical trials, time to do it better.** *Complement Ther Med.* 2008; 16(3): 121-3.

[15] Shapiro AK, Shapiro E. *The Powerful Placebo.* Baltimore: The Johns Hopkins University press, 1997

[16] White K, Kando J, Park T, Waternaux C, Brown WA. **Side effects and the "blindability" of clinical drug trials.** *Am J Psychiatry.* 1992; 149(12):1730-1.

[17] Turner JA, Jensen MP, Warms CA, Cardenas DD. **Blinding effectiveness and association of pretreatment expectations with pain improvement in a double-blind randomized controlled trial.** *Pain*. 2002; 99(1-2):91-9.

[18] Basoglu M, Marks I, Livanou M, Swinson R **Double-blindness procedures, rater blindness, and ratings of outcome. Observations from a controlled trial.** *Arch Gen Psychiatry* 1997; 54(8): 744-8

[19] Hrobjartsson A, Forfang E, Haahr MT, Als-Nielsen B, Brorson S. **Blinded trials taken to the test: an analysis of randomized clinical trials that report tests for the success of blinding.** *Int J Epidemiol.* 2007; 36:654–63.

[20] Fergusson D, Glass KC, Waring D, Shapiro S. **Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials.** *BMJ.* 2004; 328:432.

[21] Vase L, Robinson M, Verne G and Price DD, **The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation,** *Pain* 105 (2003):17–25.

[22] Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME. **Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients.** *Pain*. 2007 ; 127(1-2):63-72.

[23] Grenfell RF, Briggs AH, Holland WC. **A double-blind study of the treatment of hypertension.** *J Am Med Assoc* 1961; 176:124–8.

[24] Traut EF, Passarelli EW. **Placebos in the treatment of rheumatoid arthritis and other rheumatic conditions.** *Ann Rheum Dis* 1957; 16: 18–21.

[25] Thomas M, Eriksson SV, Lundeberg T. **A comparative study of diazepam and acupuncture in patients with osteoarthritis pain: a placebo controlled study.** *Am J Chin Med* 1991;19:95–100.

[26] Kirsch I, Weixel LJ. **Double-blind versus deceptive administration of a placebo.** *Behav Neurosci.* 1988; 102(2): 319-23.

[27] Colloca L, Lopiano L, Lanotte M, Benedetti F. **Overt versus covert treatment for pain, anxiety, and Parkinson's disease.** *Lancet Neurol.* 2004; 3(11):679-84.

[28] Hróbjartsson A, Gøtzsche PC. **Placebo interventions for all clinical conditions.** *Cochrane Database Syst Rev.* 2010; 20(1):CD003974.

[29] Gazzaniga M (ed.) *Cognitive Neuroscience*: MIT Press, 2009: 1294.

[30] Bode S, He AH, Soon CS, Trampel R, Turner R, Haynes JD. **Tracking the unconscious generation of free decisions using ultra-high field fMRI.** *PLoS One.* 2011; 6(6):e21612

[31] Soon CS, Brass M, Heinze HJ, Haynes JD. **Unconscious determinants of free decisions in the human brain.** *Nat Neurosci.* 2008; 11(5):543-5.

[32] Haynes JD, Rees G. **Predicting the stream of consciousness from activity in human visual cortex.** *Curr Biol.* 2005; 15(14):1301-7.

[33] Demos KE, Kelley WM, Ryan SL, Davis FC, Whalen PJ. **Human Amygdala Sensitivity to the Pupil Size of Others.** *Cerebral Cortex* 2008; 18:2729-2734.

[34] Caryl PG, Bean JE, Smallwood EB, Barron JC, Tully L, Allerhand M. **Women's preference for male pupil-size: Effects of conception risk, sociosexuality and relationship status.** *Personality and Individual Differences* 46,2009; 4:503-508.

[35] Harrison NA, Singer T, Rotshtein P **Pupillary contagion: central mechanisms engaged in sadness processing.** *Social Cognitive and Affective Neuroscience* 2006; 1:5–17.

[36] Churchland PS. *Brain-Wise, Studies in Neurophilosophy*: MIT Press, 2002: 471.

[37] Mommaerts JL, Devroey D. **The placebo effect: how the subconscious fits in.** *Perspectives in Biology & Medicine.* 2012a; 55(1):43-58.

[38] Schulz KF, Altman DG, Moher D, Fergusson D. **CONSORT 2010 changes and testing blindness in RCTs.** *Lancet.* 2010; 375(9721):1144-6.

[39] Sackett DL. **Turning a blind eye Why we don't test for blindness at the end of our trials.** *BMJ.* 2004; 328(7448): 1136.

[40] Fergusson D, Glass KC, Waring D, Shapiro S. **Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials.** *BMJ* 2004; 328: 432 (21 February)

[41] Kolahi J, Bang H, Park J. **Towards a proposal for assessment of blinding success in clinical trials: up-to-date review.** *Community Dent Oral* Epidemiol. 2009; 37(6):477-84.

[42] Bang H, Flaherty SP, Kolahi J, Park J **Blinding assessment in clinical trials: A review of statistical methods and a proposal of blinding assessment protocol.** *Clinical Research and Regulatory Affairs.* 2010; 27:42-51.

Influence of methylphenidate treatment assumptions on cognitive function in healthy young adults in a double-blind, placebo-controlled trial

This study examines the effect of students' assumptions that they have taken MPH on their cognitive function, whether or not they have actually taken it. This is a hands-on study that opens up placebos. This article was a primary inspiration for serial treatment assumption testing (STAT).

4.12 FULL ARTICLE: Influence of methylphenidate treatment assumptions on cognitive function in healthy young adults in a double-blind, placebo-controlled trial

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Background: Increasing numbers of students use stimulants such as methylphenidate (MPH) to improve their study capacity, making them prone to subsequent prolonged drug abuse. This study explored the cognitive effects of MPH in students who either assumed they received MPH or assumed they received a placebo.

Methods: In a double-blind, randomized, placebo-controlled trial with a between-subjects design, 21 students were subjected to partial sleep deprivation, receiving no more than 4 hours sleep the night before they were tested. In the morning, they were given either a placebo or 20 mg of MPH. They then performed free recall verbal tests and Go/No-Go tasks repeatedly, their moods were evaluated using Profile of Mood States and their tiredness was assessed using a visual analog scale, with evaluation of vigilance.

Results: No significant differences were found between those subjects who received MPH and those who received a placebo. However, significant differences were found between subjects who assumed they had received MPH or had no opinion, and those who assumed they had received a placebo. At three minutes, one hour, and one day after memorizing ten lists of 20 words, those who assumed they had received MPH recalled 54%, 58%, and 54% of the words, respectively, whereas those who assumed they had received a placebo only recalled 35%, 37%, and 34%.

Conclusion: Healthy, partially sleep-deprived young students who assume they have received 20 mg of MPH experience a substantial placebo effect that improves

consolidation of information into long-term memory. This is independent of any pharmacologic effects of MPH, which had no significant effects on verbal memory in this study. This information may be used to dissuade students from taking stimulants such as MPH during their examination periods, thus avoiding subsequent abuse and addiction.

Keywords: methylphenidate, treatment assumption, placebo, cognitive functioning

Introduction

Methylphenidate

Methylphenidate (MPH) is an amphetamine analog that increases the extracellular levels of noradrenaline and dopamine in the brain by blocking their monoamine transporters. An increase in extracellular dopamine is thought to improve attention and motivation, and to cause a general increase in motor activity.[1] Noradrenaline is believed to increase wakefulness, alertness, exploratory activity, and attention, and also has an effect on mood and blood pressure.[1,2]

In spite of the emergence of newer drugs, MPH is still one of the most frequently used drugs in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents, and is recommended as first-line treatment for ADHD.[3] During the last few years, there has been a significant increase in the diagnosis of ADHD and in the corresponding prescription of stimulant drugs such as MPH.[1,4]

Reported side effects of MPH are anorexia, nausea, vomiting, stomach ache, nervousness, headache, insomnia and tachycardia; these effects increase linearly with the dose. Other adverse effects are motor and vocal tics.[5,6]

Memory improvement after amphetamine use

Several placebo-controlled studies have used free recall of word lists to examine the cognitive effects of d-amphetamine on healthy adults. These studies show that d-amphetamine does not influence short-term memory,[7-10] but does act after initial memory encoding to improve long-term verbal memory. This improvement is prolonged by administering the drug before or during consolidation, as learned information is gradually stored into long-term memory.[8]

Misuse of stimulants by college students

Recent research shows that MPH misuse is increasing among college students, as is the illicit use of other stimulants normally used to treat ADHD; some studies report a 10-fold increase in the past two decades.[6,11] University students also misuse stimulants: for example, 4% of US university students misuse MPH each year.[12] The motivations that university students cite most frequently for stimulant use are: to heighten concentration (58%), increase alertness (43%), and just to "get high" (43%) .[13]

Use of stimulants during examination periods

Many students experience high stress levels and sleep deprivation during examination periods, which may impair their cognitive abilities. Each student handles this stress differently; sports, relaxation, vitamin supplements, tea, and coffee are all popular choices. However, a probably underestimated number of students rely on stimulant drugs such as MPH to study better, making them more prone to subsequent prolonged drug abuse.[14]

It is possible that MPH may have a substantial placebo effect on students; the mere thought that they have taken something to help them study may improve their cognition. It is interesting to note that, in a number of double-blind, placebo-controlled trials in various other domains, participants who assumed they had received an active treatment showed significant better outcomes than those who assumed they had received a placebo.[15-20]

Aim of study

There are numerous studies comparing stimulants with placebo, but far fewer in study groups without ADHD. Thereupon, only a limited number of studies have investigated the placebo effects of stimulants, and only a few of these have focused

on MPH. These studies did show that the actual effectiveness of MPH did not live up to subjects' prior expectations.[21] An improvement of memory was found, but no consistent evidence for other enhancing effects was uncovered.[21] However, the placebo effect with MPH is not well characterized, despite significant and increasing MPH use and misuse. Therefore, more studies are needed to clarify this effect. To our knowledge, no studies have examined the effect of a subject's MPH "treatment assumption", ie, whether they *assume* they have received MPH or a placebo, regardless of which they have *actually* received. The aim of this double-blind, placebo-controlled study was to investigate this treatment assumption effect by comparing the cognitive performance of healthy young students who believed they had received MPH with the performance of those who thought they had received a placebo or had no opinion. Subjects were partially sleep-deprived during the study to simulate examination period conditions.

Materials and methods

Subjects

Healthy young student volunteers were recruited using posters and advertisements in the university newspaper. Participants were excluded if they suffered from diabetes mellitus, hypertension, arrhythmias, thyrotoxicosis, epilepsy, ADHD or any other disorder that could affect their ability to concentrate, such as sleep disorders or intellectual disabilities. Other exclusion criteria were as follows: pregnancy, a history of drug abuse, prior use of psychoactive substances including MPH, a history of depression, a family history of heart problems before the age of 60 years, and familial hyperlipidemia.

In total, 21 subjects were recruited, including seven males and 14 females, of mean age 23 ± 3 (range 18-33) years. All these volunteers signed an informed consent document prior to participation in the trial. They were also asked to refrain from drinking any caffeinated or alcoholic beverages and to eat no more than two pieces of fruit in the 24 hours prior to drug administration, in order to avoid any influence on their metabolism of MPH.

Study drug

The drug dose used was 20 mg of MPH in an immediate-release formulation. While this is twice the dose recommended for most therapeutic purposes, it is the most common dose used in earlier studies of the ability of MPH to enhance cognitive function in normal young adults.[21-23] Identical, unmarked capsules were used for both the drug and the placebo; these were administered orally approximately one hour before the initial study phase of free recall testing. When administered orally, MPH is absorbed almost completely, and food has little impact on this process. In both adults and children, MPH reaches a peak concentration 1.5 to 2.5 hours after ingestion of a single, immediate-release dose, and has an elimination half-life of 2 - 3.5 hours.[24, 25]

Procedure

A randomized, placebo-controlled design was used, and was blinded for participants, dispensers and outcome assessors. All subjects knew prior to enrollment that they were participating in a double-blind study that used MPH. The cognitive tests used in the trial were a free recall of words, a Go/No-Go task and a vigilance assessment. Various tests were scheduled during and immediately after the initial free recall study phase, after a one-hour delay and after a one-day delay.

The evening before they were tested, the participants reported to the laboratory at 8:30 pm. On arrival, they were asked to answer a questionnaire, in order to exclude anyone who had, in the previous 24 hours, consumed any caffeinated or alcoholic beverages, any psychoactive substances, or more than two pieces of fruit. They also completed a brief physical examination, which included measurement of their blood pressure and heart rate.

Trial conditions were designed to mimic an examination period, and thus included partial sleep deprivation. Subjects were told to remain awake until 2 am, and were given several popular games to act as cognitive distracters, ie, two pinball machines, one air hockey table, six Nintendo Wii™ consoles, a poker set, a ping-pong set, Mastermind™ and Roll-It™. Participants were also told not to eat and to drink nothing but water. At 2 am, the subjects were told to go to sleep in prepared rooms. They were then awakened at 6 am, at which time they all consumed a similar

breakfast of croissants, sandwiches, jam, milk, and water. Immediately after breakfast, their baseline blood pressure, heart rate, and body temperature were measured.

Approximately one hour before the start of free recall testing, participants were given either 20 mg of MPH or a placebo by oral administration. To determine which they should receive, they were randomized by age and gender using a computer-based minimization procedure. Of the 21 participants, 10 received a placebo and 11 were given MPH.

Prior to starting the study phase of the free recall test, participants were informed that they were going to be shown a series of words, which they must memorize for an unspecified memory test that they would be given at a later time. They were then shown ten lists, each containing 20 unrelated words. After seeing each list, they were given 2 minutes to write down as many words as they could remember from the list, in a test of their immediate free recall. The study phase lasted for approximately 35 minutes. After an additional 3 minutes, the participants were given 15 minutes to recall all 200 words, in a final free recall test. One hour after the end of the study phase, this test was repeated in a one-hour delay free recall (1HDFR), and was repeated again after one day (1DDFR). [7]

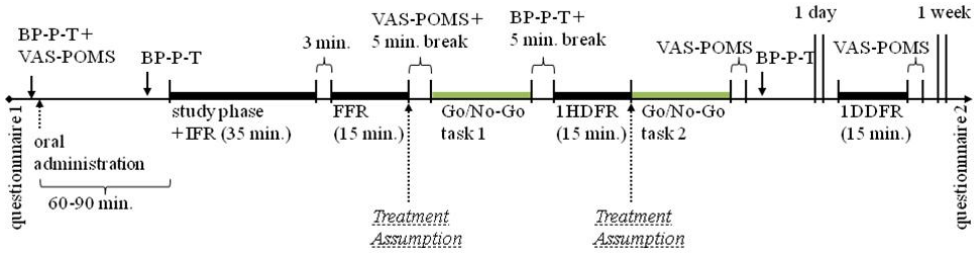
After completing the final free recall and 1HDFR, the subjects were asked what they assumed they had received, ie, a placebo, MPH or “I don’t know”. As described previously, this was their “treatment assumption”. The results of the final free call and 1HDFR were not known before their treatment assumption was questioned. Only at the end of the first day, the individual results were communicated to the participants.

The Go/No-Go task was performed twice, ie, once directly after the final free recall (approximately 2.5 hours after administration of MPH or a placebo) and the second time directly after the 1HDFR (approximately 3.5 hours after administration). In both cases, each participant’s blood pressure, heart rate, and body temperature were measured directly afterwards. The schematic overview of the experimental procedure is shown in **Figure 1**.

Word lists

For free recall testing, ten lists of 20 unrelated Dutch words were used. These were taken from a previous cognitive experiment with d-amphetamine.[7] Each word had one syllable and consisted of three to five letters. The 200 words were matched in frequency, following norms developed by Uit den Boogaart.[26] These words were presented in the center of a computer screen at a constant rate of 4 seconds per word. The order of the words was randomized, but the same presentation order was used for all participants.[7] During testing, subjects incorrectly "recalled" words that were not actually included in any ten-word lists. These words were counted in this study and referred to as intrusions. The short-term memory recency effect was investigated by analyzing how well subjects recalled the last five words in each word list. The long-term memory recency effect was investigated by doing the same with the first five words in each word list.

Figure 1: Schematic overview of the procedure of the experiment. SEE FILE: FIGURE1.ppt



BP-P-T: blood pressure - heart rate (pulse) - body temperature; IFR: immediate free recall; FFR: final free recall; 1HDFR: 1 h delay free recall; 1DDFR: 1day delay free recall; VAS: Visual Analogue Scale; POMS: Profile of Mood States; MPH: methylphenidate

Go/No-Go task

To measure a participant's capacity for sustained attention and response control, a target-detection Go/No-Go task was replicated from earlier studies.[23,27,28] Each subject was required to watch a computer screen that displayed a random series of

two-digit numbers; each number was shown for 200 milliseconds and was followed by a 700 millisecond interstimulus interval. A *target* (Go) occurred when any number appeared twice in a row. During this task, which lasted approximately 21 minutes, one quarter of the numbers were targets. When a target (Go) appeared, the subjects were instructed to press any key on the keyboard as quickly as possible. They had to suppress this response when there was no target (No-Go). The computer registered how quickly participants responded to each Go target, from the time the target appeared until the time a key was pressed, as well as the number of correct hits. Reaction times were recorded to the nearest millisecond.

Vigilance assessment

Vigilance is the ability to maintain attention and alertness over a prolonged period of time. To assess this, the reaction times from the last 3 minutes of both Go/No-Go task runs were examined. The computer recorded these reaction times in milliseconds.[23, 29]

Subjective state tests

The profile of Mood States (POMS) was used to record the subjective state of each participant and a visual analogue scale (VAS) was used to measure tiredness. POMS consists of 51 adjectives, which subjects must rate on a scale of 0 to 4. These adjectives can be subdivided into the following variables: tension, depression, anger, fatigue, and vigor.[29] For the VAS, a 100 millimeter horizontal line was used, anchored by the descriptors “not tired” at the left end (0) and “exhausted” (100) at the right end. Subjects used this VAS to rate the question “How tired/fatigued do you feel right now?”.[30,32] The response value was measured in millimeters from the left end of the scale. Participants completed the POMS and VAS tests before drug administration, and at approximately 2 hours, 4 hours, and one day later.

Pretest and post-test questionnaire

When the participants arrived on the evening before testing, they were asked what they had eaten and drunk during the last 24 hours. Their weight and height were also noted, along with any sports they played and the number of hours they exercised each week. One week after the experiment, the participants were asked

via email about the methods they used to memorize and recall the words in the free recall test.

Ethical approval.

The ethics committee of the University Hospital of Brussels, Vrije Universiteit Brussel, approved the experimental design of this study.

Statistical analysis

To assess the influence of treatment assumption on cognitive function, the study population was divided into three main groups based on their treatment assumption: placebo (subjects who assumed they had received a placebo when asked); MPH (subjects who assumed they had received MPH); and DNK (subjects who had no opinion, ie, "did not know"). A one-way analysis of variance was used to compare the participants who assumed they had taken a placebo with those who assumed they had taken MPH or said that they did not know. A criterion alpha level of 0.05 was used throughout the analyses.

Results

General results.

The protocol was completed by 21 volunteers. On arrival, none of them had a blood pressure greater than 140/90 mmHg or an irregular heart rate. The characteristics of the population are shown in **Table 1.** No significant effects on cognition were observed between the MPH and the placebo group when comparing the immediate and delayed free recalls, Go/No-Go tasks, or vigilance tasks after administration of placebo or 20 mg of MPH. Subjects from both study groups remembered 42% of the words during the final free recall (right after study phase) and 44% during the 1HDFR. After the final free recall, subjects from the MPH group had 221 correct hits for the Go/No-Go task compared with 231 correct hits in the placebo group (p=0.057); the vigilance test also did not show any significant differences in reaction times between the groups. According to our study results, MPH does not improve consolidation into long-term memory in healthy young adults with short-term sleep deprivation. Because there was no significant difference in performance between

those on MPH and those on placebo, the treatment groups were combined and the results were reanalyzed by treatment assumption.

Table 1: Population characteristics, correctness of assumptions, and distribution of the stu population, categorized by treatment assumption.

	Treatment assumption[a] after FFR (n=21)			**Treatment assumption[a] after 1HDFR** (n=21)		
	Placebo (n=12)	MPH (n=4)	DNK (n=5)	Placebo (n=15)	MPH (n=2)	DNK (n=4)
Men	4	1	2	6	1	0
Women	8	3	3	9	1	4
Mean age, years (sD)	24 (4)	22 (3)	20 (2)	23 (4)	21 (3)	21 (2)
Mean weight,kg (sD)	61 (8)	66 (8)	66 (8)	62 (9)	64 (8)	64 (8)
Treatment assumed correctly	6	2	-	8	1	-
Treatment assumed wrongly	6	2	-	7	1	-
DnK	-	-	5	-	-	4

Note: [a]Treatment assumption means that subjects were asked if they assumed they had receiv placebo or MPH.

Abbreviations: MPH, methylphenidate; DNK, do not know; FFR, free recall at three minutes after stu
phase; 1HDFR, one-hour delay free recall; SD, standard deviation.

Free recall

Table 2 shows the mean number of words that subjects recalled correctly out of 200, depending on their treatment assumptions at final free recall and again at 1HDFR. Subjects who reported "MPH" or "DNK" after final free recall remembered significantly more words at final free recall, 1HDFR and 1DDFR than those who reported "Placebo". There were no significant differences between those who reported "MPH", "DNK" or "Placebo" after 1HDFR, although the numbers still showed the same trend. These results, especially for treatment assumption after final free recall, contrast with the results from the *real* MPH and placebo groups, which showed no significant differences in correct word recall.

Table 2: Number of correctly recalled words categorized by treatment assumption after FF
treatment assumption after 1HDFR, and actual treatment

	Treatment assumption after FFR[a] (n=21)				**Treatment assumption after 1HDFR** (n=21)			
	Placebo (n=12)	MPH (n=4)	DNK (n=5)	ANOVA	Placebo (n=15)	MPH (n=2)	DNK (n= 4)	ANOVA
Mean number of correctly recalled words								
iFR (sD)	111(24)	140 (35)	130 (19)	P(2) > 0.05 P* > 0.05 P** > 0.05	117(26)	132 (24)	131 (35)	P(2) > 0.05 P* > 0.05 P** > 0.05

FFR (sD)	70 (21)	108 (32)	100 (22)	P(2) = 0.01 P* = 0.015 P** = 0.018	78 (26)	99 (22)	102 (34)	P(2) > 0.05 P* > 0.05 P** > 0.05
1hDFR (sD)	73 (22)	115 (31)	103 (24)	P(2) = 0.01 P* = 0.009 P** = 0.025	80 (26)	103 (17)	110 (37)	P(2) > 0.05 P* > 0.05 P** > 0.05
1DDFR (sD)	67 (24)	107 (35)	108 (17)	P(2) < 0.01 P* = 0.021 P** = 0.004	76 (29)	98(28)	109 (32)	P(2) > 0.05 P* > 0.05 P** > 0.05

Notes: P*. P-value comparing placebo with Mph; P**. P-value comparing placebo with DnK; P(2) value comparing placebo, MPH, and DNK with two degrees of freedom.

Abbreviations: ANOVA, analysis of variance; SD, standard deviation; MPH, methylphenidate; DNK not know; FFR, free recall at three minutes after study phase; 1HDFR, one-hour delay free recall; 1D one-day delay free recall.

Number of intrusions

Analysis showed that treatment assumptions made no significant difference to the number of intrusions. Furthermore, there were no significant differences in intrusions between the *real* MPH and placebo groups.

Recency and primacy effects

Subjects recalled the last five words significantly better in the immediate free recall than in the final free recall, 1HDFR or 1DDFR, since the words were still in short-term memory (Table 3). All applicable P-values were significant. In general, subjects who reported a treatment assumption of MPH or DNK recalled the last five words much

better than those who assumed placebo. There was, however, no difference between the *real* MPH and placebo groups.

The long-term memory primacy effect was studied by comparing how well subjects recalled the first five and last five words in each word list, as shown once again in **Table 3**.

In the final free recall, 1HDFR, and 1DDFR, subjects recalled approximately twice as many of the first five words, in comparison with the last five words. In most cases, subjects whose treatment assumption was MPH or DNK recalled the first five words much better than those who assumed they had received a Placebo. Again, there were no significant differences between the *real* MPH and placebo groups. Subjects reported their treatment assumptions after final free recall and again after 1HDFR, but similar recency and primacy results were found no matter which set of treatment assumptions was used.

Table 3: Effects of recency and primacy, categorized by treatment assumption

	Treatment assumption after FFR (n=21)				**Treatment assumption after 1HDFR** (n=21)			
	Placebo (n=12)	MPH (n=4)	DNK (n=5)	ANOVA	Placebo (n=15)	MPH (n=2)	DNK (n=4)	ANOVA
IFR				P(2) < 0.01 P* = 0.002 P** = 0.045				P(2) < 0.05 P* < 0.05 P** < 0.05
First 5 words recall % (sD)	68 (6)	81 (6)	75 (6)		70 (6)	77 (6)	75 (8)	
Last 5 words	58 (6)	71 (10)	72 (3)	P(2) < 0.01	61 (7)	62 (11)	74 (6)	P(2) = 0.015

recall % (sD)				P* = 0.007 P** ⩾ 0.001				P* ⩽ 0.05 P** = 0.004
FFR First 5 words recall % (sD)	47 (8)	65 (8)	60 (8)	P(2) ⩾ 0.01 P* = 0.002 P** = 0.008	51 (8)	58 (10)	59 (9)	P(2) ⩽ 0.05 P* ⩽ 0.05 P** ⩽ 0.05
Last 5 words recall % (sD)	22 (4)	42 (7)	44 (3)	P(2) ⩾ 0.01 P* ⩾ 0.001 P** ⩾ 0.001	27 (6)	38 (7)	44 (6)	P(2) ⩾ 0.01 P* = 0.029 P** = 0.001
1HDFR First 5 words recall % (sD)	50 (8)	76 (7)	65 (8)	P(2) ⩾ 0.01 P* ⩾ 0.001 P** = 0.003	54 (9)	69 (8)	68 (10)	P(2) = 0.016 P* = 0.041 P** = 0.015
Last 5 words recall% (sD)	24 (4)	45 (6)	46 (5)	P(2) ⩾ 0.01 P* ⩾ 0.001 P** ⩾ 0.001	28 (6)	39 (4)	47 (7)	P(2) ⩾ 0.01 P* = 0.025 P** ⩾ 0.001
1DDFR First 5 words recall % (sD)	47 (9)	71 (8)	66 (6)	P(2) ⩾ 0.01 P* ⩾ 0.001 P** ⩾ 0.001	52 (10)	67 (12)	65 (6)	P(2) = 0.028 P* ⩾ 0.001 P** ⩾ 0.001

Last 5 words recall % (sD)	23 (5)	41 (9)	48 (2)	P(2) ≤ 0.01 P* = 0.068 P** = 0.025	28 (7)	32 (8)	49 (6)	P(2) ≤ 0.01 P* ≤ 0.05 P** ≤ 0.001

Notes: P(2), P-value comparing placebo, MPH, and DNK with two degrees of freedom; P*, P-va
comparing placebo with Mph; P**, P-value comparing placebo with DnK.

Abbreviations: ANOVA, analysis of variance ; SD, standard deviation; MPH, methylphenidate; DNK
not know; FFR, free recall at three minutes after study phase; 1HDFR, one-hour delay free recall;
not significant.

Go/No-Go task

Subjects performed the target detection Go/No-Go task twice, at 2.5 and 3.5 hours after administration of the drug. It should be noted that the results from two subjects (a man and a woman) were excluded, due to an error in data recording.

During this 21-minute task, the drug did not influence the outcome. The *real* MPH and placebo groups performed similarly, registering 221 and 231 hits, respectively, in the Go/No-Go task that was performed after 2.5 hours; the corresponding reaction times were 347 and 345 milliseconds. Treatment assumption also made no significant difference.

Vigilance assessment

The reaction times from the last 3 minutes of both Go/No-Go tasks were used to evaluate vigilance. Results from two subjects were excluded, as in the Go/No-Go task. In the second Go/No-Go task, subjects whose treatment assumption after final free recall was DNK were on average 69 milliseconds slower than those who assumed Placebo (P=0.02); this was not expected . There was no significant

difference between those who assumed they had received Placebo after final free recall and those who assumed MPH. No significant differences were found between the *real* MPH and placebo groups.

Subjective responses

The POMS results showed an alteration in subjective mood the day after administration. Participants whose treatment assumption after final free recall was MPH showed significantly more anger (P = 0.031) and fatigue (P = 0.036) than those who answered Placebo. This was not seen using the second set of treatment assumptions reported after 1HDFR. The VAS scale, which measured fatigue, was not affected by assumed treatment. Again, no significant differences were found between the *real* MPH and placebo groups.

Accuracy of treatment assumption

Only two people (18%) who had received MPH guessed correctly after final free recall; this declined to one person (9%) after 1HDFR. Of the subjects who received a placebo, 60% guessed correctly after final free recall; this rose to 80% after 1HDFR. Subjects who received the active drug were almost three times less accurate in their guesses after final free recall than those who received the placebo, and they were six times less accurate after 1HDFR. Subjects who said they did not know what they had received were not taken into account (**Table 1**).

Post-test questionnaire

Of the 21 subjects, 20 answered all the questions, and one subject did not respond and was excluded from the analysis. Of these 20, 14 (70%) said that they had relied on their physical signs to determine whether they had received MPH or a placebo. Two participants (10%) said they had relied on the results they expected on the immediate free recall and final free recall to guess whether or not they had taken the drug. Four (20%) said they had relied on both their physical signs and their expected results.

Discussion

This double-blind study was designed to explore whether the *assumption* that they received MPH or a placebo had an effect on cognition in healthy young adults. It explicitly investigated whether MPH and/or the assumption of having taken MPH had a facilitating effect on memory consolidation processes and reaction times under the short-term sleep deprivation conditions typically associated with an examination period. To the best of our knowledge, this is the first study that has examined the effects of MPH treatment assumptions in healthy volunteers.

Interpretation of the results

The effect of the treatment assumption reported by participants directly after final free recall was significant. Participants who *assumed* they had received MPH or who had no opinion recalled more words than those who *assumed* they had received a placebo. At the same time, there was no significant difference in word recall between those who *really* received MPH and those who did not, either on this test or on any of the other tests. Therefore, the enhanced word recall was due to differences in the subjects' treatment assumptions, and not to the drug that they took.

Several studies have shown that MPH can have an effect on mood arousal.[33,34] In the present study, the *assumption* that they had taken MPH had a noticeable impact on subjects' anger and fatigue levels 24 hours after administration, whereas the *actual* treatment taken had no effect.

Participants in double-blind, randomized, placebo-controlled trials can experience treatment effects that lead to unblinding.[19] For example, headaches caused by calcium channel blockers can make some participants suspect that they received the active study drug. The present study shows that assessing participants' treatment assumptions in a randomized controlled trial can also yield important information when it is not immediately evident that participants have been unblinded by the treatment effects or side effects.[19]

Subjects who performed more confidently on the free recall tests in this study might have assumed subsequently that they had received MPH rather than a placebo; this possibility was addressed to a certain extent by the post-test questionnaire. It might also have been valuable to ask subjects about their treatment assumptions prior to final free recall, and to assess how confident participants felt about their

performances in the free recall tests. However, given that this study showed that *actual* administration of MPH did not have a significant effect on free recall test results or generate any physical signs, it follows that the administration of MPH did not unblind the participants. The fact that some subjects said in the post-test questionnaire that they had relied on physical signs or expected results to guess their treatment is compatible with post-test rationalization.

Study limitations

Some caution is in order when interpreting the findings of this research. This study has a between-subjects design in which participants were given either a placebo or MPH. A counterbalanced, within-subject design with a one-week wash-out period might have been preferable as it could have reduced the effect of differences between individuals. However, this was not possible due to resource constraints.Because of recruitment problems, there were only 21 volunteers in the study. Therefore, findings that were not statistically significant may have been so due to a small sample size. Tests were repeated several times using the same material, including during and immediately after the free recall study phase and several times later on. Therefore, it could be argued that the observed effects were partially caused by influences on the memory retrieval process. This was also noted by Zeeuws et al[7, 8, 10] and Soetens et al.[9] In their study, the use of immediate recall tests did not affect the influence of d-amphetamine on delayed recall.[10] Because of the similar activity of MPH and d-amphetamine, it can be argued that this is likely to be true for MPH as well.

One should also keep in mind that intersubject variability exists with MPH. It is rapidly and extensively absorbed after oral administration, and differences in metabolism as well as pharmacodynamic drug interactions can induce differences in bioavailability, as can nutrition effects such as high or low fat diets and associated gastric emptying times.[1,35]

Subjects were not forced to choose a treatment assumption. With hindsight, it would have been better to let subjects choose between MPH, placebo and DNK, and then force them to choose between the first two. This should probably be the case in all studies which solicit treatment assumptions. Finally, a possible explanation for the lack of difference between MPH and placebo might be that the dose was too

low. Alternatively the tests used may not be the particularly good tests of MPH effects in the study population.

Future research

Repeating the above study using sequential dosing of MPH or placebo would be an interesting and useful future line of research. The results of this study might lead one to conclude that students who *assumed* they had taken MPH during an examination period would experience more memory enhancement than those who *actually* took MPH. "Treatment assumption" is closely related to the placebo effect, which is thought to be associated with a spectrum of factors including expectancy, hope, conditioning and anxiety reduction.[36] Nonblinded studies comparing placebos with no treatment options may contribute to a better appreciation of the full effect of placebos.[37]

Additional research with a larger study population is needed to elucidate better the precise nature of "treatment assumption". Future trials with longer follow-up and larger study populations may also clarify the effects of MPH treatment assumption in healthy subjects, especially when combined with an understanding of subjects' prior expectations about treatment efficacy.

Conclusion

This study showed that the *assumption* of having received a single dose of 20 mg dose of MPH may induce a substantial placebo effect in healthy young students, improving consolidation of information into long term memory. Students who thought they were given the drug recalled 54%-58% of the word lists, while those who thought they had received the placebo recalled only 34-37%. This is independent of any pharmacological effects of MPH which in this study had no significant effects on verbal memory. This information may be used to dissuade students from taking stimulants such as MPH during their examination periods, thus avoiding one trap towards becoming addicted subsequently.[38,39] In addition to this, pointing towards the placebo effect indicates to students that they have the

psychological means within themselves to enhance their own study capacity without any need for drugs.

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Disclosure

The authors report no conflicts of interest in this work.

References

[1] Rang HP, Dale MM, Ritter JM, Flower RJ: *Rang and Dale's pharmacology.* Philadelphia: Elsevier; 2008.

[2] Volkow ND, Swanson JM: **Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD.** *Am J Psychiatry.* 2003, 160(11): 1909-18.

[3] De Sousa A, Kalra G: **Drug therapy of attention deficit hyperactivity disorder: current trends.** *Mens Sana Monogr*. 2012, 10(1): 45-69.

[4] Setlik J, Bond GR, Ho M. **Adolescent prescription ADHD medication abuse is rising along with prescriptions for these medications.** *Pediatrics*. 2009, 124(3): 875-80.

[5] Heal DJ, Pierce DM: **Methylphenidate and its isomers: their role in the treatment of attention-deficit hyperactivity disorder using a transdermal delivery system.** *CNS Drugs.* 2006, 20(9): 713-38.

[6] Klein-Schwartz W: **Abuse and toxicity of methylphenidate.** *Curr Opin Pediatr.* 2002, 14(2): 219-23.

[7] Zeeuws I, Soetens E: **Verbal memory performance improved via an acute administration of D-amphetamine.** *Hum Psychopharmacol.* 2007, 22(5): 279-87.

[8] Zeeuws, I, Deroost N, Soetens E: **Effect of an acute d-amphetamine administration on context information memory in healthy volunteers: evidence from a source memory task.** *Hum Psychopharmacol.* 2010, 25(4): 326-34.

[9] Soetens E, Casaer S, D'Hooge R, Hueting JE: **Effect of amphetamine on long-term retention of verbal material.** *Psychopharmacology (Berl).* 1995, 119(2): 155-62.

[10] Zeeuws I, Deroost N, Soetens E: **Verbal memory improved by D-amphetamine: influence of the testing effect.** *Hum Psychopharmacol.* 2010, 25(5): 377-87.

[11] Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, Utzinger L, Fusillo S: **Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature.** *J Am Acad Child Adolesc Psychiatry.* 2008, 47(1): 21-31.

[12] Bogle KE, Smith BH: **Illicit methylphenidate use: a review of prevalence, availability, pharmacology, and consequences.** *Curr Drug Abuse Rev.* 2009, 2(2): 157-76.

[13] Teter CJ, McCabe SE, Cranford JA, Boyd CJ, Guthrie SK: **Prevalence and motives for illicit use of prescription stimulants in an undergraduate student sample.** *J Am Coll Health.* 2005, 53(6): 253-62.

[14] Barrett SP, Darredeau C, Bordy LE, Pihl RO **Characteristics of Methylphenidate Misuse in a University Student Sample** *Can J Psychiatry* 2005, 50:457–461

[15] Lewis TL, Karlowski TR, Kapikian AZ, Lynch JM, Shaffer GW, George DA, Chalmers TC. **A controlled clinical trial of ascorbic acid for the common cold.** *Ann NY Acad Sci.* 1975, 258: 505– 512.

[16] McRae C, Cherin E, Yamazaki TG, Diem G, Vo AH, Russell D, Ellgring JH, Fahn S, Greene P, Dillon S, Winfield H, Bjugstad KB, Freed CR. **Effects of perceived treatment on quality of life and medical outcomes in a double-blind placebo surgery trial.** *Arch Gen Psychiatry.* 2004, 61: 412–420.

[17] Bausell R, Lao L, Bergman S, Lee W-L, Berman BM. **Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials.** *Eval Health Prof.* 2005, 28: 9–26.

[18] Dar R, Stronguin F, Etter J-F. **Assigned versus perceived placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers.** *J Consult Clin Psychol.* 2005, 73: 350–353.

[19] Colagiuri B, Morley KC, Boakes RA, Haber PS. **Expectancy in double-blind placebo-controlled trials: an example from alcohol dependence.** *Psychother Psychosom.* 2009, 78: 167–171.

[20] Thomas JL, Guo H, Lynam IM, Powell JN, Okuyemi KS, Bronars CA, Ahluwalia JS. **The impact of perceived treatment assignment on smoking cessation outcomes among African-American smokers.** *J Gen Intern Med.* 2008, 23: 1361–1366.

[21] Repantis D, Schlattmann P, Laisney O, Heuser I: **Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review.** *Pharmacol Res.* 2010, 62(3): 187-206.

[22] Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Wong C, Ma J, Pradhan K, Benveniste H, Swanson JM. **Methylphenidate decreased the amount of glucose needed by the brain to perform a cognitive task.** *PLoS One.* 2008, 16;3(4): e2017.

[23] Camp-Bruno JA, Herting RL: **Cognitive effects of milacemide and methylphenidate in healthy young adults.** *Psychopharmacology (Berl).* 1994, 115(1-2): 46-52.

[24] Sachdev PS, Trollor JN: **How high a dose of stimulant medication in adult attention deficit hyperactivity disorder?** *Aust N Z J Psychiatry.* 2000, 34(4): 645-50.

[25] Kowalik S, Minami H, Silva R: **Dexmethylphenidate extended-release capsules for the treatment of attention deficit hyperactivity disorder.** *Expert Opin Pharmacother.* 2006, 7(18): 2547-57.

[26] Uit den Boogaart PC: *Woordfrequenties in geschreven en gesproken Nederlands.* Utrecht: Oosthoek, Scheltema & Holkema; 1975.

[27] Fillmore MT, Blackburn JS, Harrison EL: **Acute disinhibiting effects of alcohol as a factor in risky driving behavior.** *Drug Alcohol Depend.* 2008, 95(1-2): 97-106.

[28] Ostling EW, Fillmore MT: **Tolerance to the impairing effects of alcohol on the inhibition and activation of behavior.** *Psychopharmacology (Berl).* 2010, 212(4): 465-73.

[29] Childs E, de Wit H: **Subjective, behavioral, and physiological effects of acute caffeine in light, nondependent caffeine users.** *Psychopharmacology (Berl).* 2006, 185(4): 514-23.

[30] Insana SP, Montgomery-Downs HE: **Maternal postpartum sleepiness and fatigue: associations with objectively measured sleep variables.** *J Psychosom Res.* 2010, 69(5): 467-73.

[31] Wilhelm B. Kellert R, Schnell R, Lüdtke H, Petrini O: **Lack of sedative effects after vespertine intake of oxazepam as hypnotic in healthy volunteers.** *Psychopharmacology (Berl).* 2009, 205(4): 679-88.

[32] Elliott,R, Sahakian BJ, Matthews K, Bannerjea A, Rimmer J, Robbins TW: **Effects of methylphenidate on spatial working memory and planning in healthy young adults.** *Psychopharmacology (Berl).* 1997, 131(2): 196-206.

[33] Hermens DF, Cooper NJ, Clark CR, Debrota D, Clarke S.D, Williams LM: **An integrative approach to determine the best behavioral and biological markers of methylphenidate.** *J Integr Neurosci.* 2007, 6(1): 105-40.

[34] Elliott WJ: **Drug interactions and drugs that affect blood pressure.** *J Clin Hypertens (Greenwich).* 2006, 8(10):731-7.

[35] Schlösser R, Nenadic I, Wagner G, Zysset S: **Koch K, Sauer H:. Dopaminergic modulation of brain systems subserving decision making under uncertainty: a study with fMRI and methylphenidate challenge.** *Synapse* 2009, 63: 429–442.

[36] Mommaerts JL, Devroey D. **The placebo effect: how the subconscious fits in.** *Perspectives in Biology & Medicine.* 2012, 55(1): 43-58.

[37] Hróbjartsson A, Kaptchuk TJ, Miller FG. **Placebo effect studies are susceptible to response bias and to other types of biases.** *J Clin Epidemiol.* 2011, 64(11): 1223-9.

[38] [No authors listed]. Methylphenidate: abuse in Europe. *Prescrire Int*.2013;22(135):47.

[39] Tagaya H. Methylphenidate: pharmacology, indication and potential of abuse. *Nihon Rinsho*. 2010;68(8):1550-1555.Japanese.

Psyche, Soma and Seizures: Mind-Body Non-Dualism Changes the Whole Picture

This article discusses how the mind/body divide has engendered a millennia-long dispute that is still ongoing in the domain of epilepsy. At present, this has led to inappropriate medication-based therapy for many PNES patients. An alternative view of this may bring many benefits. In areas such as this, it becomes completely evident how important it is to take into account the very philosophical issue that lies at the center of this thesis.

4.13 FULL ARTICLE: Psyche, Soma and Seizures: Mind-Body Non-Dualism Changes the Whole Picture

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Abstract

The domain of seizures, like many other medical domains, is still plagued by Cartesian dualism, in which mind and brain are viewed as distinct entities even when looked upon as forming integral parts of a larger whole. Both physicians and patients come to the consultation room with this mindset. As a direct consequence, seizures are largely classified as organic, psychogenic or of mixed nature and are treated as such. However, the reality in this matter is non-dualistic. Hereby, a different landscape emerges for the domain of seizures, in which psyche and soma basically coincide. This new landscape is in several ways more patient-friendly. As to the management of seizures, there are substantial consequences involved, putting the whole patient in a respectful way at the center of care.

Keywords

epilepsy, PNES, mind/brain non-dualism, epileptic discharge versus charge, psychosomatic medicine, dissociative disorders

Main Article

Introduction

"We should not inquire whether psyche and body are one thing, any more than whether the wax and its imprint are, or in general whether the matter of each thing is one with that of which it is the matter." (from Aristotle, De Anima)

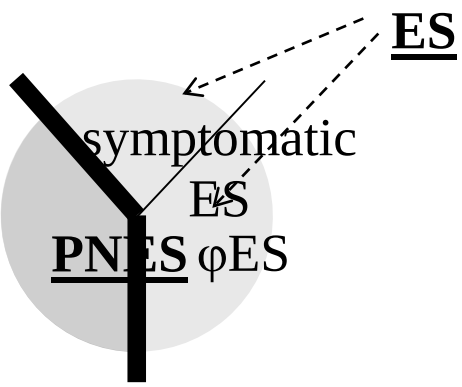
One can ask whether the cause of any mind/brain product is 'psychological' (a thought, feeling or image) or 'physical' (a neuronal change), but mind/brain non-dualism holds it is both. There is no causality: both change *at exactly the same time* and therefore are not distinct entities. Even when a change in one part of the brain causes a subsequent change in another part, the mind (mental processing, consciously and/or subconsciously) and brain (making abstraction of other involved bodily changes for the sake of the argument) change in unison at each discrete step of the process. Numerous studies demonstrate this, most notably with vision.[1,2]

However, mind/brain non-dualism is not reductionist materialism, since it does not *reduce* the mind to the brain. To clarify this, think of a painting. This consists entirely of paint, yet if we exclusively focus on the paint, we miss the art. Likewise, by concentrating on the brain, we miss the mind in it. Unfortunately, this happens in many medical domains, including seizures.

In this article, we address the consequences of mind/brain non-dualism for epilepsy.

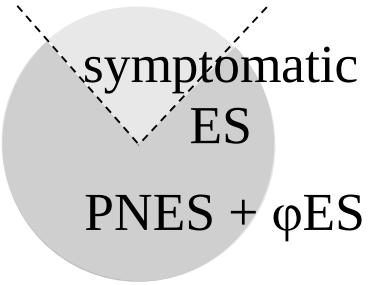
Differential diagnosis of ES and PNES (see Figure 1a & 1b)

Figure 1a: Depiction of the current categorization of the seizures domain for the sake of this article



This figure shows the currently used segmentation of epilepsy, in which ES = 'symptomatic ES' (i.e. with a distinctively organic etiology) + φES (avoiding the confusing term 'functional', cf. infra), and stands in stark contrast to PNES. Note that our view is about a different categorization, in which one area is formed by PNES and φES, if not also to some smaller degree by symptomatic ES. This can, with some exaggeration perhaps, be depicted as:

Figure 1b: Depiction of our categorization of the seizures domain for the sake of this article



Psychogenic non-epileptic seizures (PNES) are "episodes of movement, sensation, or behaviors that are similar to epileptic seizures but that do not have [pathological] neurologic origin… Video-EEG monitoring is preferred for diagnosis".[3] About 3 million people in the US have diagnosed seizures, of which 10% to 20% are thought to have PNES. Up to 40% of seizure patients in general neurology clinics may have PNES,[4] and 10% of PNES patients may also have epileptic seizures (ES).[5]

φES (cf. fig. 1) = without any known organic etiology, yet presently (but not by us) thought to be "organically, thus not psychologically caused." We prefer to not use the term 'functional' because to some authors (but not all), 'functional ES' = PNES + φES. We use 'φES' as symbol for the sake of this article, in order to transcend with this the fuzzy notion of 'functional'. Some debate is possible about where cryptogenic and genetically influenced epilepsies belong.

Many neurologists see PNES and φES as different, just as the mind and brain are seen as different. The latter is not true, so is the former?

PNES as well as φES symptoms vary widely and are highly overlapping.[6] Isolated signs such as self injury, incontinence, psychological tests, patient history, and ambulatory EEG are not sufficient for differential diagnosis,[3,7-9] nor is tongue biting or pseudo-status epilepticus.[6] In one study, no PNES patients had seizures while sleeping, whereas in another 60% did – with eyewitnesses confirming most cases.[10] Reported PNES psychological risk factors include school difficulties, family discord, interpersonal conflicts and physical abuse.[11,12] Obesity, chronic pain, anxiety and post-traumatic stress syndrome are also implicated.[4] However, it is unclear whether these are causes or consequences. Moreover, a cerebral pathology is common in PNES,[6] as is psychopathology in φES.[13] The latter includes the situation during childhood, when behavioral disturbances are up to 4.8 times more frequent than in the general juvenile population. There is also a high rate of psychiatric diagnoses,[14] although no psychological profile seems to help.

In one study, epileptologists only attained a maximum specificity of 50% when asked to differentiate φES and nonepileptic events based solely on seizure descriptions.[15] Another study searched for specific indicators that accurately differentiated PNES from φES, but found that only ictal stuttering and the 'teddy bear' sign (age-inappropriate behavior) were adequately reliable and specific to PNES.[16] However, both had low sensitivity, suggesting they were specific to one small PNES subset. Laboratories also offer no solution, since prolactin serum tests give many false positives, therefore are performed less and less.[8] PNES diagnoses frequently take years, evidence that differential diagnosis is hard without video-EEG, with over-reliance on specific clinical features creating diagnostic errors. Top epileptologists agree that differentiating φES and PNES on clinical grounds remains challenging: "Diagnostic humility is essential when considering PNES.".[4]

Even the value of ictal video-EEG is uncertain, since its inter-rater reliability is relatively low,[7,17] with the latter authors highlighting "the difficulties and subjective

components inherent to this diagnosis (of PNES) … the 'art' of medicine or a subjective component to the diagnosis of seizures is part of neurologic practice." While the raters lacked a history, they should not have needed it if video-EEG is a 'gold standard'. Notably, psychiatrists rate video-EEG accuracy for PNES diagnosis significantly lower than do neurologists ($p < 0.001$).[18] The stressful setting and accompanying expectations of video-EEG can also cause symptoms resembling PNES, even in patients without behavioral disorders. Furthermore, muscle and motion artifacts can obscure EEGs or lead to false identification of epileptiform discharges.[4] Non-specific EEG changes are often misinterpreted as evidence of φES, with EEG over-interpretation being a key reason for misdiagnosis.[19]

Problems with the definition of PNES and φES

There is, however, an even deeper problem. Many authors[20,21] take positions such as: "Psychogenic nonepileptic seizures superficially resemble epileptic seizures, but are not associated with ictal electrical discharges in the brain".[7] Epilepsy is thus defined as seizures plus ictal epileptiform EEG abnormalities (IEA) by *agreed convention,* without evidence of it being a *natural kind phenomenon*. To clarify this, consider three random characteristics: blue eyes (BE), long nose (LN) and curly hair (CH). One can talk of BE-LN-CH syndrome and even distinguish it from its green-eyed counterpart, but it has no natural basis. More generally, a test C that *defines* the difference between the one and the other does not prove the difference is meaningful.

Note again that this paper only addresses seizures *without* a distinctively organic etiology (i.e. 'symptomatic ES' such as due to a brain tumor). Some of these non-'symptomatic ES' include IEA, are currently called 'epileptic seizures' and are deemed to be *organic* although with no *known* distinctively organic etiology. Other non-'symptomatic ES' do not include IEA and are therefore currently called '*psychogenic* non-epileptic seizures'. However, we assert there is no reason for this organic versus psychogenic distinction based on IEA, apart from a prior assumption of mind/brain dualism. We do not ignore the agreed convention, but do question whether it has meaning (by analogy with BE-LN-CH syndrome). It might be better to rename φ*ES* as 'IEA^{POS} seizures' and PNES as 'IEA^{NEG}-seizures', avoiding the impression that φ*ES* is a 'real' disease and PNES is not.

Conversely, difficult differential diagnosis does not prove φES and PNES are similar or identical. Birthmarks and melanomas are difficult to distinguish superficially, yet they are different. Unlike birthmarks and melanomas, however, there is no known anatomopathological difference between φES and PNES. They are only seen as different *because* they lie on opposite sides of the mind/body divide, despite scientific consensus that this divide does not exist. Epilepsy in its broadest historical sense has always traversed this imaginary line,[22] and is still an unfortunate example of Cartesian dualism.

Symptom modeling may play a role in PNES. 66% of PNES patients in one study[23] admitted that they had witnessed a seizure prior to their own seizure onset, compared to 11% of ES patients. However, only 25% consented to be interviewed when contacted by telephone, and many more had PNES than ES. ES patients started seizures at a younger age, and therefore had fewer opportunities to witness seizures prior to onset. The study also depended on self-reporting without third-party corroboration, which may have influenced results, since ES patients may have a vested interest in concealing information that endangers their ES diagnosis. Furthermore, there was no significant difference in familial seizure prevalence between ES and PNES patients, suggesting both conditions may have the same predisposing factors and etiology.

Currently, there is no integrated PNES biopsychosocial model and "most of what we know is derived from retrospective studies open to all biases associated with 'data trawling'".[7] Neuroimaging has not made a significant contribution to PNES understanding, and there is a surprising contrast between observed PNES seizure behavior and subjective experiences – links between ictal mental states and seizure manifestations are not well understood.

Many questions remain about PNES,[7] especially with children.[24] Meanwhile, difficult differential PNES diagnosis has led to a mean latency of 7.2 years between manifestation and diagnosis,[4,25,26] and 75% to 80% of patients are being treated with AEDs,[27] using higher doses than those used for φES patients [28] – and creating more side effects.[8]

Indications of a 'psychological' nature for *ϕ*ES

In one study of 89 epilepsy patients, 64% believed stress increased seizure frequency.[29] In another study of 100 diagnosed but poorly controlled cases,[30] over 90% identified at least one factor that precipitated seizures, the most common being stress. Others included depression, tiredness, menstrual cycles, overexcitement and happiness. 65% reported one or more low-risk factors, such as being relaxed, engaged in mental activity, or having a constant arousal level. 15% reported they could induce seizures, while 60% reported they could sometimes consciously abort impending seizures – usually by relaxing. In a third study, stress (beta=0.25, P<0.01), anxiety (beta=0.30, P<0.01) and depression (beta=0.30, P<0.01) predicted change in epileptic seizure recency, with depression mediating the relationship between stress/anxiety and seizure recency/frequency changes.[31]

There is significant evidence of a complex bidirectional relationship between mood disorders and epilepsy.[32,33] Patients with a mood disorder history are also twice as likely to develop pharmacoresistant epilepsy[33] and a history of depression prior to epilepsy onset predicts seizures that are more poorly controlled with pharmacotherapy and surgery.[34] In addition, a strong bidirectional relation between schizophrenia and epilepsy has been found in England,[35] Finland[36] and Taiwan,[37] implying a shared susceptibility that may arise from genetic, environmental and neurobiologic factors. In the Taiwanese study, schizophrenia patients were six time more likely to have epilepsy, and epilepsy patients were seven times more likely to have schizophrenia.

Other studies show the role of suggestion. In one study, participants received a hypnotic suggestion to have a seizure. Surprisingly, 16 (34%) had epileptic events, showing that hypnosis may provoke φES.[38] In another study, 20 ES patients were given a placebo infusion they were told induced seizures. Two experienced typical epileptic events, and three had atypical events, showing placebo-based suggestion can provoke ES.[39]

Charge and discharge in the brain

Many complex, interacting pathophysiological mechanisms lead to seizures. In most, a local area of the brain becomes prone to seizures when pools of neurons surrounding a focus become sufficiently excited for seizure activity to spread.[40]

Generalized seizures occur when cortical excitability allows thalamic recruiting volleys to spread due to precipitating factors such as sleep deprivation, depression, and serotonin and glutamate levels, with one study showing stress (49.5%), lack of sleep (35.5%), and fatigue (32.5%) are most common.[41] Increasing seizure proneness can result from mounting excitability or temporary changes in intrinsic seizure vulnerability thresholds, which may be localized to neurons near the focus.

In this paper, 'charge' denotes relative proneness to seizure (mounting excitation and/or excitability), and 'discharge' refers to the actual seizure. Using this concept, PNES and φES can be brought together in a hypothesis that, as will be explained, fits all known data points.

In this view, several charge and discharge patterns are possible (see Figure 2):

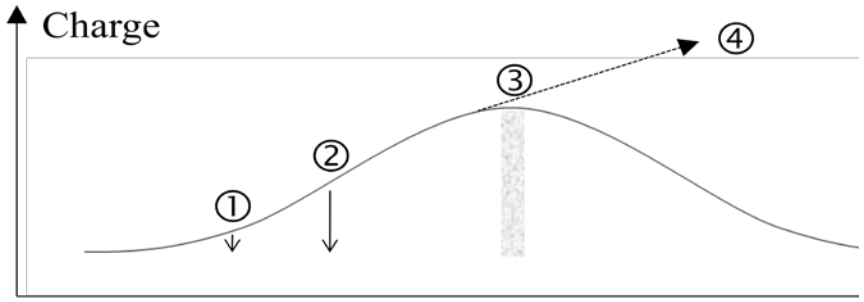
1. There is evidence that some charges discharge quickly with minimal build-up and no clinical seizures. First, a study of 19 autistic children found 6 had interictal epileptiform EEG abnormalities but no clinical seizures, even when there were focal/multifocal sharp waves and generalized spike-wave complexes.[41] Second, 20% to 25% of PNES patients have interictal epileptiform EEG activity without seizures, including spike-and-wave discharges,[6] as do 15% of the general population.[8] Third, there is an unresolved controversy whether interictal epileptic discharges differ from ictal discharges or are very brief seizures.[42] The latter corresponds with the second pattern below, but the answer to the controversy may vary by seizure and syndrome type. In general, it appears that full-blown seizures do not occur without sufficient charge.

2. Some charges build up and discharge in 'cathartic' events with specific EEG phenomena typically lasting 1 to 2 minutes. This may be due to unstable neurons becoming the epicenter of a spreading 'electrical storm'.[43] This instability of these neurons may result from genetic defects, brain damage, tumors and/or metabolic problems, although many seem idiopathic.[43] This is classical ES, where a seizure can be thought of as a spike (or other phenomenon) that turns into a full-blown event.[44] Note that AEDs reduce seizures in most patients, but have little effect on spikes,[45] showing spikes do not cause seizures without charge.

3. Some charges do not discharge suddenly and cannot be seen on an EEG. These may persist for 1 to 2 hours,[46] corresponding to PNES. Although an EEG shows nothing, it is incorrect to say that nothing is happening in the brain and therefore PNES is due to the mind. Also note that a scalp EEG is particularly insensitive, so it is possible that discharges may be identified in future as techniques advance.

4. This may be a psychotic insult (discussed later).

Figure 2: Possible patterns of discharge in seizures with no clear organic etiology



Possible 'patterns of discharge'
① Very quick discharge without any significant charge or any seizures
② Strong sudden discharge following more buildup of charge (ES)
③ Non-EEG discharge, where a longer (and stronger) buildup of charge is possible (PNES)
④ Psychotic insult?

The timeframes for (2) and (3) are consistent with φES and PNES. Note that according to this, a discernible EEG discharge may enhance a seizure, but also end it more quickly. The distinction between φES and PNES may lie in how the brain reacts electrophysiologically to charge, which may be the cause of both. Moreover, many patients feel a discharge is imminent before a seizure, supporting the existence of charge. This is analogous to other conditions where the mind/brain readies itself, such as migraine, narcolepsy, orgasm or falling asleep. Thus, the concept of charge is not unique to epilepsy.

Interestingly, the literature appears to put forward the following two different notions:

- psychological stress -> **no IEA** -> PNES
- psychological stress [-> biochemistry] -> **IEA** -> φES

An example of the latter is when severe distress elevates steroid levels, and these "elevated steroid levels accelerate epileptogenesis and lower seizure threshold in various animal models for epilepsy".[47] Here, biochemistry is seen as the cause of IEA, and the event is deemed organic and categorized as φES, with psychological stress only a modulator. However, without IEA, psychological stress is seen as the cause and the seizure is categorized as PNES. Hence, IEA *by itself* determines whether the seizure is deemed to be of organic or psychogenic origin. An *agreed convention* is being used to explain what was agreed previously, resulting in circular and incorrect logic.

Our view fits all available data while providing a complete non-dualistic approach. It answers many other questions about PNES and φES, including why PNES seizures last longer, why differential diagnosis is difficult, why PNES has a poorer prognosis, why both are statistically correlated, why patients with ES due to an anatomical cause do not have *continuous* seizures, why 20% to 30% of φES patients are pharmacoresistant, why AEDs have a large placebo effect, and why seizure remission alone does not indicate a good outcome. Of course, these questions can be answered from a dualistic standpoint, but the mind and brain are not separate.

The distinction between φES, PNES and normal brain function is not clear-cut. For instance, over 10% of healthy individuals show nonspecific EEG abnormalities and 0.5% have epileptiform discharges.[4] Epileptiform discharges can occur during acute barbiturate or benzodiazepine withdrawal in healthy people.[48] Also, about 70% of PNES cases occur during the second to fourth decade, which is the valley of a bimodal ES age curve.[4] This is consistent with the view that seizures which do not develop into ES persist as PNES.

While normal brain rhythm function is not well understood, activating artificial (software) neural network nodes through pulses rather than stochastically helps avoid information loops and chaos. Therefore, normal rhythms may help avoid chaos in the brain. This may also be why we need stronger rhythms when attentive, since we are processing more information and thus are more prone to chaos. Seizures seem to lie at one extreme of normal rhythms, when a simultaneous

activation overshoot occurs. The fact that 7% to 10% of the general population has at least one epileptic seizure during their lifetime supports this notion.[49] This epileptic discharge results from trying to cope with chaos overload, with vulnerability to chaos arising from known risk factors. Repeated chaos may harm the brain, necessitating such a coping mechanism.

Another possibility is that chaos vectors could point in all directions, cancelling each other out so that an EEG appears normal. If so, the 'normal' PNES-EEG may prove abnormal in the future with more precise EEG technology. Even today, stereo EEG using depth electrodes can show semi-continuous or continuous epileptic activity subcortically during interictal psychosis even while a scalp EEG is negative.[50]

Despite earlier optimistic findings,[51] recent EEG studies have failed to predict the onset of (any kind of) seizures.[52] However, many patients know when a seizure is likely, although they can rarely specify an exact time. In one study of 562 subjects, over 50% experienced clinical prodromes or auras.[53] Other clinical findings supporting a pre-seizure state are increased cerebral blood flow,[54] blood-oxygen-level-dependent (BOLD) signals[55] and heart rate changes.[56] Additionally, characterizing interactions between brain regions by measuring relationships between recording sites has shown promise for seizure prediction.[52] All of these observations support the existence of charge, whether or not the prodromes are seen as part of the seizures themselves.

If discharge is a physiological coping mechanism, its presence or absence as such may be *the* difference between φES and PNES. As an analogy, consider a person with an infection and related fever, and another person with the same infection but a high fever resulting in seizures and urinary incontinence. The underlying disease is the same, but the high fever brings side effects. Similarly the φES coping mechanism may have side effects such as tongue biting and urinary incontinence.

Without φES discharge, PNES may have detrimental effects that result in more psychiatric symptoms, a view supported by growing insights into a broad spectrum of interictal psychotic episodes,[57] along with recent genetic research implicating epilepsy and psychotic illness as outcomes of common etiological processes.[36] The nature of charge and the neurophysiological underpinnings of psychosis are both unknown, but intriguingly, one may shed light upon the other (see "psychotic insult" in Figure 2). It is interesting that new schizophrenia treatments combine neuroleptics and antiepileptics,[58] and that anticonvulsants are also used increasingly to treat bipolar disorders[59] as well as other neurological and psychiatric conditions.[60]

Lessons from kindling

'Kindling' is the mild periodic stimulation of a brain focus using electrical stimulation or convulsive agents.[61] This leads to progressive intensification of motor seizures, which are first elicited and then spontaneous. This has been demonstrated in rats, cats, dogs and baboons, and in many brain sites.

Frequent kindling leads to emotionality and interictal behavior disturbances similar to those in certain forms of epilepsy[61] and PNES. Personality disorders occur in 45% of PNES patients, with emotionally unstable personality disorders predominating in 32%.[62] This may be why PNES has a poor long-term prognosis.[27] One study[63] showed that 12 years after manifestation and 4.1 years after diagnosis, 71% of PNES patients still had seizures and 56.4% depended on social security, with dependency increasing in subsequent follow-ups.

Given kindling's discovery in 1969, it is surprising how little attention its conditioning effects have received. One investigation[61] found environmental and temporal conditioning in rats, both for seizures and interictal behavior. Thus, increases in seizures and interictal behavior disturbances may have conditioned and unconditioned components, a very important consideration for the management of seizures.

A new landscape and practical consequences

With new epilepsy knowledge emerging, classifications need to be updated regularly. As with any classification, many patients do not fit in any slot and many more evolve over the years.[64] Epilepsy is now leading a convergence of psychiatry and neurology, showing that cerebral function is profoundly influenced by psychological and social factors.[22]

We envisage a new non-dualistic landscape where φES, PNES and malingering may still play a role, but where there are many more gradations and overlaps. A person may experience diverse events and even change position in this landscape due to kindling-like mechanisms. Indeed, studies show that as to the present-day classification, PNES occurs in 3.6% to 10.8% of ES patients, and ES occurs in 12% to 36% of PNES sufferers.[8]

This may lead to the development and use of mental hygiene methods that reduce charge and discharge in ES and PNES patients. It is intriguing that some people can abort seizures psychologically, especially when slow development of seizures gives time for countermeasures such as relaxation or concentration. Furthermore, seizures do not appear to propagate when a majority of involved neurons cannot be recruited,[65] representing a lack of charge. Evidence also shows children can both inhibit *and* generate seizures spontaneously.[66] One study[67] showed epileptic patients generally scored poorly for internal health locus of control, and those who scored higher could frequently control their seizures. Therefore, it is important to help patients understand that seizures are not necessarily random, but related to feelings, actions and thoughts.[40]

Another relevant factor is that PNES may be an *involuntary* expression of psychological distress.[7,68,69] E.g. unconscious rage, fear, and helplessness directed at a dominant and abusive 'male' culture may help explain why PNES is three times more prevalent in women.[70] Some authors speak of 'dissociative seizures' (e.g. as in reading a book and not hearing one's name) or suggest stress as a precipitating factor, even if it is unrelated to current circumstances and the patient is barely aware of it.[8]

In this landscape, *all* seizure patients can benefit from appropriate mental hygiene, including those whose seizures have a clearly organic etiology. Patients may generally comply more readily with a mental hygiene approach that does not imply psychological illness, since many equate 'no physical cause' with 'all in the mind'[7] and ultimately with 'guilt' – increasing their desire for a purely organic diagnosis. Among other things, mental hygiene may involve working through this conscious or subconscious feeling of guilt. The conditioning effect of kindling may also diminish if patients know they are able to abort an attack, and may also reduce the helplessness that they feel when they view their affliction as purely physical and therefore only susceptible to physical treatment.

Many PNES patients can talk and follow commands during seizures, and only have seizures when witnesses are present or when they are not being recorded.[71] Unfortunately, this leads to suspicion of malingering, currently only distinguished from PNES by a patient's 'confession'. It may be more valid to accept a grey area, with self-deception lying between these two extremes.[8] Cognitive neuroscience has increasingly highlighted the importance of this grey area when showing the tremendous power of subconceptual processing.[1]

Some literature points to the utility of controlled clinical trials involving EEG neurofeedback. This approach may be desirable, "but perhaps the most important variable determining the success of neurofeedback is the clinician's ability to instill a motivation to succeed in the patient"[72] requiring well-trained and motivationally adept professionals.

Few studies have addressed psychological ES and PNES treatment, and their methodologies are poor,[73] including small size, mixed/unclear diagnoses, variable follow-up, and lack of definite conclusions.[74] They have provided limited evidence that psychological treatment is effective[26] and, even with fairly good immediate outcomes, 56% to 80% of patients relapse after 18 to 24 months, with similar results after 5 years.[75-77] Despite therapy, 25% to 33% of patients become chronic.[26,78] One search for psychological epilepsy treatments[79] in the Cochrane Epilepsy Group's Specialized Register (July 2005), Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2005), and MEDLINE (1966 to March 2005) concluded that there was no reliable evidence for effective treatment, in view of methodological deficiencies and small study populations.

Many psychotherapeutic approaches seem similarly effective with seizures,[7] much as they do with many other conditions.[80,81] This does not mean they are inactive,[82] but that they act mainly through *non-specific factors* not yet very well understood,[83-85] as scientifically proven in many domains.[86,87] A strong argument has been made that these factors operate at the non-conceptual level and combine the placebo effect and empathy.[88,89] Mental hygiene approaches may need to appropriately address this non-conceptual dimension to be truly helpful.

One important part of mental hygiene is the way a PNES diagnosis is communicated.[26] Since this can be powerfully suggestive, it needs to strike a balance between appropriate care and emphasizing the patient's power to help themselves. While PNES is 'beyond voluntary control' in many cases,[90] that is not sufficient to call it a conversion disorder. Many things beyond voluntary control operate subconceptually, and it is logical to support patients at this level.

AEDs are used increasingly for treatment, but epidemiological evidence shows they only treat symptoms and do not prevent epileptogenesis (structural and functional changes contributing to epilepsy progression).[44] There is a pressing need for alternative strategies,[91] since there is no real cure other than surgical removal of the epileptic focus in relevant cases. The current strategy is to find the lowest AED dosage that makes life comfortable and meaningful, but prolonged usage has very

negative side effects,[92] with new side effects reported regularly.[93] Many authors[92,94,95] conclude that withdrawal of anticonvulsant medication should be considered when an epileptic patient has been free of seizures for 2 years. However, 12% to 66% of patients in remission for at least 2 years relapse during or after AED withdrawal, with the highest relapse rates in the 12 months following withdrawal.[94] A strong emphasis on mental hygiene may reduce these rates, and also help the 20% to 30% of epilepsy patients who do not respond to AEDs.[96]

Many confirmed PNES patients remain on AEDs,[97] fearing their driving license will be revoked. 20% to 44% remain on one or more AEDs,[27] which is similar to high percentages seen in other 'medically unexplained' syndromes.[98] The adverse effects of environmental expectations are an important reason for this,[99] with patients stuck in a dualistic trap. Sadly, even patients who stop using AEDs because of a PNES diagnosis often resume due to family pressures.[75] Patients can also become hostile when their diagnosis changes from ES to PNES,[100] which is especially understandable when the PNES diagnosis is made by exclusion, a negative process resulting in non-diagnosis.[101]

Even while sharing an organic etiology, some patients develop ES whereas others do not. This indicates that some are more vulnerable, potentially due to an underlying condition that is part of this new landscape. This does not mean ES patients are psychiatric patients, but it does mean they may be able to help themselves and be helped using psychological means. Thus, that which is important for φES may be important for ES as a whole.

Last but not least, seizure remission is not by itself a complete measure of a good outcome. Nearly half of PNES patients who become seizure free remain unproductive. Many continue to show severe psychopathological symptoms,[102] and more than 50% remain on social security 11 years after seizure onset.[62] Furthermore, PNES behavior is plastic and can shift to another complaint following treatment.[103] Therefore, one needs to consider health-related quality of life, employment status, physical morbidity, mortality and other factors[104] when evaluating outcomes, not just seizure reduction. For example, in one study, there was no clear relationship between quality of life and seizure reduction, except when PNES ceased completely.[104] Therefore, seizure control should not be the only focus of treatment. A strong emphasis on mind/brain non-dualism provides a more holistic approach.

Conclusion

The current view of φES and PNES is still dominated by mind/brain dualism, hampering efforts to reach other insights and practical approaches. We contend that φES and PNES do not lie on opposite sides of a non-existent mind/brain divide. From a non-Cartesian standpoint, the only difference is then an EEG phenomenon that may be a coping mechanism, rather than a direct reflection of the underlying disorder. Taking this view, epilepsy may enter a new landscape where dualistic borders become fuzzy, and even the distinction between normal and abnormal becomes more flexible – removing an age-old stigma. This new landscape may be more natural and patient-friendly, since it puts the whole patient at the center of care. It is our view that profound mental hygiene based on non-dualistic principles may then naturally play a prominent part in the lives of all seizure patients. Let us not just look at the paint, but also at the art of the painting.

References

1. Gazzaniga MS. *The cognitive neurosciences.* 4th ed. Cambridge, Mass.: MIT Press; 2009:1294.
2. Churchland PS. *Brain-wise : studies in neurophilosophy.* Cambridge, Mass.: MIT Press; 2002: 471.
3. Alsaadi TM, Marquez AV. Psychogenic nonepileptic seizures. *American family physician.* 2005;72(5):849-856.
4. Devinsky O, Gazzola D, LaFrance WC, Jr. Differentiating between nonepileptic and epileptic seizures. *Nature reviews. Neurology.* 2011;7(4):210-220.
5. Benbadis SR, Agrawal V, Tatum WO. How many patients with psychogenic nonepileptic seizures also have epilepsy? *Neurology.* 2001;57(5):915-917.
6. Kuyk J, Leijten F, Meinardi H, Spinhoven, Van Dyck R. The diagnosis of psychogenic non-epileptic seizures: a review. *Seizure: the journal of the British Epilepsy Association.* 1997;6(4):243-253.

7. Reuber M. Psychogenic nonepileptic seizures: answers and questions. *Epilepsy & behavior : E&B.* 2008;12(4):622-635.

8. Mellers JD. The approach to patients with "non-epileptic seizures". *Postgraduate medical journal.* 2005;81(958):498-504.

9. Auxemery Y, Hubsch C, Fidelle G. Psychogenic non epileptic seizures: a review. *L'Encephale.* 2011;37(2):153-158.

10. Duncan R, Oto M, Russell AJ, Conway P. Pseudosleep events in patients with psychogenic non-epileptic seizures: prevalence and associations. *Journal of neurology, neurosurgery, and psychiatry.* 2004;75(7):1009-1012.

11. Patel H, Scott E, Dunn D, Garg B. Nonepileptic seizures in children. *Epilepsia.* 2007;48(11):2086-2092.

12. Duncan R, Oto M. Predictors of antecedent factors in psychogenic nonepileptic attacks: multivariate analysis. *Neurology.* 2008;71(13):1000-1005.

13. Schwartz JM, Marsh L. The psychiatric perspectives of epilepsy. *Psychosomatics.* 2000;41(1):31-38.

14. Austin JK, Caplan R. Behavioral and psychiatric comorbidities in pediatric epilepsy: toward an integrative model. *Epilepsia.* 2007;48(9):1639-1651.

15. Deacon C, Wiebe S, Blume WT, McLachlan RS, Young GB, Matijevic S. Seizure identification by clinical description in temporal lobe epilepsy: how accurate are we? *Neurology.* 2003;61(12):1686-1689.

16. Hoerth MT, Wellik KE, Demaerschalk BM, et al. Clinical predictors of psychogenic nonepileptic seizures: a critically appraised topic. *The neurologist.* 2008;14(4):266-270.

17. Benbadis SR, LaFrance WC, Jr., Papandonatos GD, et al. Interrater reliability of EEG-video monitoring. *Neurology.* 2009;73(11):843-846.

18. Harden CL, Burgut FT, Kanner AM. The diagnostic significance of video-EEG monitoring findings on pseudoseizure patients differs between neurologists and psychiatrists. *Epilepsia.* 2003;44(3):453-456.

19. Brown RJ, Syed TU, Benbadis S, LaFrance WC, Jr., Reuber M. Psychogenic nonepileptic seizures. *Epilepsy & behavior : E&B.* 2011;22(1):85-93.

20. Mari F, Di Bonaventura C, Vanacore N, et al. Video-EEG study of psychogenic nonepileptic seizures: differential characteristics in patients with and without epilepsy. *Epilepsia.* 2006;47 Suppl 5:S64-S67.

21. Wood BL, Haque S, Weinstock A, Miller BD. Pediatric stress-related seizures: conceptualization, evaluation, and treatment of nonepileptic seizures in children and adolescents. *Current opinion in pediatrics.* 2004;16(5):523-531.

22. Reynolds EH, Trimble MR. Epilepsy, psychiatry, and neurology. *Epilepsia.* 2009;50 Suppl 3:S50-S55.

23. Bautista RE, Gonzales-Salazar W, Ochoa JG. Expanding the theory of symptom modeling in patents with psychogenic nonepileptic seizures. *Epilepsy & behavior : E&B.* 2008;13(2):407-409.

24. Bhatia MS, Sapra S. Pseudoseizures in children: a profile of 50 cases. *Clinical pediatrics.* Sep 2005;44(7):617-621.

25. Reuber M, Fernandez G, Bauer J, Helmstaedter C, Elger CE. Diagnostic delay in psychogenic nonepileptic seizures. *Neurology.* 2002;58(3):493-495.

26. Bodde NM, Brooks JL, Baker GA, Boon PA, Hendriksen JG, Aldenkamp AP. Psychogenic non-epileptic seizures--diagnostic issues: a critical review. *Clinical neurology and neurosurgery.* 2009;111(1):1-9.

27. Reuber M, Elger CE. Psychogenic nonepileptic seizures: review and update. *Epilepsy & behavior : E&B.* 2003;4(3):205-216.

28. Benbadis SR. How many patients with pseudoseizures receive antiepileptic drugs prior to diagnosis? *European neurology.* 1999;41(2):114-115.

29. Haut SR, Vouyiouklis M, Shinnar S. Stress and epilepsy: a patient perception survey. *Epilepsy & behavior : E&B.* 2003;4(5):511-514.

30. Spector S, Cull C, Goldstein LH. Seizure precipitants and perceived self-control of seizures in adults with poorly-controlled epilepsy. *Epilepsy research.* 2000;38(2-3):207-216.

31. Thapar A, Kerr M, Harold G. Stress, anxiety, depression, and epilepsy: investigating the relationship between psychological factors and seizures. *Epilepsy & behavior : E&B.* 2009;14(1):134-140.

32. Kanner AM, Balabanov A. Depression and epilepsy: how closely related are they? *Neurology.* 2002;58(8 Suppl 5):S27-39.

33. Kanner AM. Mood disorder and epilepsy: a neurobiologic perspective of their relationship. *Dialogues in clinical neuroscience.* 2008;10(1):39-45.

34. Kanner AM. Depression in epilepsy: a complex relation with unexpected consequences. *Current opinion in neurology.* 2008;21(2):190-194.

35. Wotton CJ, Goldacre MJ. Coexistence of schizophrenia and epilepsy: record-linkage studies. *Epilepsia.* 2012;53(4):e71-74.

36. Clarke MC, Tanskanen A, Huttunen MO, Clancy M, Cotter DR, Cannon M. Evidence for shared susceptibility to epilepsy and psychosis: a population-based family study. *Biological psychiatry.* 2012;71(9):836-839.

37. Chang YT, Chen PC, Tsai IJ, et al. Bidirectional relation between schizophrenia and epilepsy: a population-based retrospective cohort study. *Epilepsia.* 2011;52(11):2036-2042.

38. Khan AY, Baade L, Ablah E, McNerney V, Golewale MH, Liow K. Can hypnosis differentiate epileptic from nonepileptic events in the video/EEG monitoring unit? Data from a pilot study. *Epilepsy & behavior : E&B.* 2009;15(3):314-317.

39. Walczak TS, Williams DT, Berten W. Utility and reliability of placebo infusion in the evaluation of patients with seizures. *Neurology.* 1994;44(3 Pt 1):394-399.

40. Fenwick P. The behavioral treatment of epilepsy generation and inhibition of seizures. *Neurologic clinics.* 1994;12(1):175-202.

41. Sperling MR, Schilling CA, Glosser D, Tracy JI, Asadi-Pooya AA. Self-perception of seizure precipitants and their relation to anxiety level, depression, and health locus of control in epilepsy. *Seizure : the journal of the British Epilepsy Association.* 2008;17(4):302-307.

42. Bernasconi A, Bernasconi N, Bernhardt BC, Schrader D. Advances in MRI for 'cryptogenic' epilepsies. *Nature reviews. Neurology.* 2011;7(2):99-108.

43. Orme-Johnson D. Evidence that the Transcendental Meditation program prevents or decreases diseases of the nervous system and is specifically beneficial for epilepsy. *Medical hypotheses.* 2006;67(2):240-246.

44. Walker MC, White HS, Sander JW. Disease modification in partial epilepsy. *Brain : a journal of neurology.* 2002;125(Pt 9):1937-1950.

45. Frei MG, Zaveri HP, Arthurs S, et al. Controversies in epilepsy: debates held during the Fourth International Workshop on Seizure Prediction. *Epilepsy & behavior : E&B.* 2010;19(1):4-16.

46. Thompson NC, Osorio I, Hunter EE. Nonepileptic seizures: reframing the diagnosis. *Perspectives in psychiatric care.* 2005;41(2):71-78.

47. Joels M. Stress, the hippocampus, and epilepsy. *Epilepsia.* 2009;50(4):586-597.

48. Fernandez-Torre JL. De novo absence status of late onset following withdrawal of lorazepam: a case report. *Seizure : the journal of the British Epilepsy Association.* 2001;10(6):433-437.

49. Bear MF, Connors BW, Paradiso MA. *Neuroscience : exploring the brain.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.

50. Elliott B, Joyce E, Shorvon S. Delusions, illusions and hallucinations in epilepsy: 2. Complex phenomena and psychosis. *Epilepsy research.* 2009;85(2-3):172-186.

51. Litt B, Echauz J. Prediction of epileptic seizures. *Lancet neurology.* 2002;1(1):22-30.

52. Mormann F, Andrzejak RG, Elger CE, Lehnertz K. Seizure prediction: the long and winding road. *Brain : a journal of neurology.* 2007;130(2):314-333.

53. Rajna P, Clemens B, Csibri E, et al. Hungarian multicentre epidemiologic study of the warning and initial symptoms (prodrome, aura) of epileptic seizures. *Seizure : the journal of the British Epilepsy Association.* 1997;6(5):361-368.

54. Weinand ME, Carter LP, el-Saadany WF, Sioutos PJ, Labiner DM, Oommen KJ. Cerebral blood flow and temporal lobe epileptogenicity. *Journal of neurosurgery.* 1997;86(2):226-232.

55. Federico P, Abbott DF, Briellmann RS, Harvey AS, Jackson GD. Functional MRI of the pre-ictal state. *Brain : a journal of neurology.* 2005;128(Pt 8):1811-1817.

56. Kerem DH, Geva AB. Forecasting epilepsy from the heart rate signal. *Medical & biological engineering & computing.* 2005;43(2):230-239.

57. Adachi N, Akanuma N, Ito M, Okazaki M, Kato M, Onuma T. Interictal psychotic episodes in epilepsy: duration and associated clinical factors. *Epilepsia.* 2012;53(6):1088-1094.

58. Theochari I, Boulas C, Chaidemenos A. [Use of antiepileptic drugs in schizophrenia: A review of recent evidence]. *Psychiatrike = Psychiatriki.* 2007;18(3):259-272.

59. Grunze HC. Anticonvulsants in bipolar disorder. *Journal of mental health.* 2010;19(2):127-141.

60. Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS drugs.* 2008;22(1):27-47.

61. Barnes SJ, Pinel JP. Conditioned effects of kindling. *Neuroscience and biobehavioral reviews.* 2001;25(7-8):745-751.

62. Hovorka J, Nezadal T, Herman E, Nemcova I, Bajacek M. Psychogenic non-epileptic seizures, prospective clinical experience: diagnosis, clinical features, risk factors, psychiatric comorbidity, treatment outcome. *Epileptic disorders : international epilepsy journal with videotape.* 2007;9 Suppl 1:S52-S58.

63. Reuber M, Pukrop R, Bauer J, Helmstaedter C, Tessendorf N, Elger CE. Outcome in psychogenic nonepileptic seizures: 1 to 10-year follow-up in 164 patients. *Annals of neurology.* 2003;53(3):305-311.

64. Reynolds EH, Rodin E. The clinical concept of epilepsy. *Epilepsia.* 2009;50 Suppl 3:S2-S7.

65. Wolf P. The role of nonpharmaceutic conservative interventions in the treatment and secondary prevention of epilepsy. *Epilepsia.* 2002;43 Suppl 9:S2-S5.

66. Fenwick PB. The relationship between mind, brain, and seizures. *Epilepsia.* 1992;33 Suppl 6:S1-S6.

67. Asadi-Pooya AA, Schilling CA, Glosser D, Tracy JI, Sperling MR. Health locus of control in patients with epilepsy and its relationship to anxiety, depression, and seizure control. *Epilepsy & behavior : E&B.* 2007;11(3):347-350.

68. LaFrance WC, Jr., Devinsky O. Treatment of nonepileptic seizures. *Epilepsy & behavior : E&B.* 2002;3(5 Suppl):S19-S23.

69. Gates JR (1998) Diagnosis and treatment of nonepileptic seizures. In: McConnell H, Snyder PJ, editors. *Psychiatric comorbidity in epilepsy : basic mechanisms, diagnosis, and treatment.* 1st ed. Washington, DC: American Psychiatric Press; 1998: 187-204.

70. Rosenbaum M. Psychogenic seizures--why women? *Psychosomatics.* 2000;41(2):147-149.

71. Iriarte J, Parra J, Urrestarazu E, Kuyk J. Controversies in the diagnosis and management of psychogenic pseudoseizures. *Epilepsy & behavior : E&B.* 2003;4(3):354-359.

72. Sterman MB, Egner T. Foundation and practice of neurofeedback for the treatment of epilepsy. *Applied psychophysiology and biofeedback.* 2006;31(1):21-35.

73. Brooks JL, Goodfellow L, Bodde NM, Aldenkamp A, Baker GA. Nondrug treatments for psychogenic nonepileptic seizures: what's the evidence? *Epilepsy & behavior : E&B.* 2007;11(3):367-377.

74. Ettinger AB, Devinsky O, Weisbrot DM, Ramakrishna RK, Goyal A. A comprehensive profile of clinical, psychiatric, and psychosocial characteristics of patients with psychogenic nonepileptic seizures. *Epilepsia.* 1999;40(9):1292-1298.

75. Betts T, Boden S. Diagnosis, management and prognosis of a group of 128 patients with non-epileptic attack disorder. Part II. Previous childhood sexual abuse in the aetiology of these disorders. *Seizure : the journal of the British Epilepsy Association.* 1992;1(1):27-32.

76. Farias ST, Thieman C, Alsaadi TM. Psychogenic nonepileptic seizures: acute change in event frequency after presentation of the diagnosis. *Epilepsy & behavior : E&B.* 2003;4(4):424-429.

77. O'Sullivan SS, Sweeney BJ, McNamara B. The opinion of the general practitioner toward clinical management of patients with psychogenic nonepileptic seizures. *Epilepsy & behavior : E&B.* 2006;8(1):256-260.

78. Reuber M, House AO. Treating patients with psychogenic non-epileptic seizures. *Current opinion in neurology.* 2002;15(2):207-211.

79. Ramaratnam S, Baker GA, Goldstein LH. Psychological treatments for epilepsy. *Cochrane database of systematic reviews.* 2005(4):CD002029.

80. Luborsky L, Rosenthal R, Diguer L et al. The dodo bird verdict is alive and well – mostly. *Clinical psychology: science and practice*. 2002;9(1):2-12.

81. Grencavage LM, Norcross JC. Where are the commonalities among the therapeutic common factors? *Professional psychology: research and practice*. 1990;21(15):372-378.

82. Wampold BE, Mondin GW, Moody M, Stich F, Benson K, Ahn HA. Meta-Analysis of Outcome Studies Comparing Bona Fide Psychotherapies: Empirically, "All Must Have Prizes". *Psychological Bulletin*. 1997;122(3):203-215

83. Kirsch I. Placebo psychotherapy: synonym or oxymoron? *Journal of clinical psychology.* 2005;61(7):791-803.

84. Wampold BE. Contextualizing psychotherapy as a healing practice: Culture, history and methods. *Applied and preventive psychology.* 2001;10(2):69-86.

85. Patterson CH. What is the placebo in psychotherapy? *Psychotherapy: Theory, Research, Practice, Training*. 1985; 22(2):163-169.

86. Ahn HN, Wampold BE. Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. *Journal of counseling psychology*. 48(3):251-257.

87. Joyce AS, Wolfaardt U, Sribney C, Aylwin AS. Psychotherapy research at the start of the 21st century: the persistence of the art versus science controversy. *Canadian journal of psychiatry. Revue canadienne de psychiatrie.* 2006;51(13):797-809.

88. Mommaerts JL, Devroey D. The placebo effect: how the subconscious fits in. *Perspectives in biology and medicine.* 2012;55(1):43-58.

89. Mommaerts JL, Goubert L, Devroey D. Empathy beyond the conceptual level: core nonspecific factors of psychotherapy. *Perspectives in biology and medicine.* 2012;55(2):175-182.

90. Reuber M, Jamnadas-Khoda J, Broadhurst M, et al. Psychogenic nonepileptic seizure manifestations reported by patients and witnesses. *Epilepsia.* 2011;52(11):2028-2035.

91. Halasz P, Rasonyi G. Neuroprotection and epilepsy. *Advances in experimental medicine and biology.* 2004;541:91-109.

92. Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. *Cochrane database of systematic reviews.* 2006(2):CD005003.

93. Walia KS, Khan EA, Ko DH, Raza SS, Khan YN. Side effects of antiepileptics--a review. *Pain practice : the official journal of World Institute of Pain.* 2004;4(3):194-203.

94. Specchio LM, Beghi E. Should antiepileptic drugs be withdrawn in seizure-free patients? *CNS drugs.* 2004;18(4):201-212.

95. Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years. A prospective study. *The New England journal of medicine.* 1988;318(15):942-946.

96. Strehl U, Kotchoubey B, Trevorrow T, Birbaumer N. Predictors of seizure reduction after self-regulation of slow cortical potentials as a treatment of drug-resistant epilepsy. *Epilepsy & behavior : E&B.* 2005;6(2):156-166.

97. Duncan R. The withdrawal of antiepileptic drugs in patients with non-epileptic seizures: safety considerations. *Expert opinion on drug safety.* 2006;5(5):609-613.

98. Potts SG, Bass CM. Psychosocial outcome and use of medical resources in patients with chest pain and normal or near-normal coronary arteries: a long-term follow-up study. *The Quarterly journal of medicine.* 1993;86(9):583-593.

99. Doust J, Del Mar C (2004) Why do doctors use treatments that do not work? *BMJ.* 2004;328:474-475.

100. Abubakr A, Kablinger A, Caldito G. Psychogenic seizures: clinical features and psychological analysis. *Epilepsy & behavior : E&B.* 2003;4(3):241-245.

101. Dekkers W, van Domburg P. The role of doctor and patient in the construction of the pseudo-epileptic attack disorder. *Medicine, health care, and philosophy.* 2000;3(1):29-38.

102. Reuber M, Mitchell AJ, Howlett S, Elger CE. Measuring outcome in psychogenic nonepileptic seizures: how relevant is seizure remission? *Epilepsia.* 2005;46(11):1788-1795.

103. Sirven JI, Glosser DS. Psychogenic nonepileptic seizures: theoretic and clinical considerations. *Neuropsychiatry, neuropsychology, and behavioral neurology.* 1998;11(4):225-235.

104. Quigg M, Armstrong RF, Farace E, Fountain NB. Quality of life outcome is associated with cessation rather than reduction of psychogenic nonepileptic seizures. *Epilepsy & behavior : E&B.* 2002;3(5):455-459.

Helicobacter psychologicus: Psyche Lost, Psyche Regained

This article explains how an exclusive focus on material causation can lead to an utter disregard for the psyche. Curing a 'disease' – such as PUD – without regard to the patient as a total being leads to substantial uncertainty about whether the patient actually fares better in the long run. This, of course, does not eliminate the importance of material factors – only a synthesis of all aspects of the patient will eventually lead to optimal care.

4.14 FULL ARTICLE: Helicobacter psychologicus: Psyche Lost, Psyche Regained

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Abstract

Helicobacter pylori has gained acceptance as the main cause of peptic ulcer disease. However, this may be due to a prior predilection for somatic rather than psychological causes that prefers the bacterium over the psyche and the crater over the symptoms. There are many arguments to put the psyche back on stage with the bacterium, where it may even assume the leading role. In this article, we focus on some of these arguments, which receive little attention elsewhere, and make the case for managing the entire psychosocial situation rather than just the ulcer.

Keywords

Helicobacter pylori; peptic ulcer disease; functional dyspepsia; causal thinking; stress; psychosomatic etiology

Main Article

Ulcer or symptoms?

The elements of peptic ulcer disease (PUD) are a peptic ulcer (or crater) and symptoms that overlap those of dyspepsia (nausea, vomiting, anorexia, fullness and bloating, abdominal discomfort and pain). The ulcer is seen as the cause of the symptoms, which is even evident in the name of the disease: peptic **u**lcer disease (P**U**D). Clinical signs and symptom are not seen as enough to diagnose PUD reliably [1], with such diagnosis requiring technical methods, most notably endoscopy. The crater takes precedence, so much so that articles minimize the role of symptoms and “Patients who present with typical dyspepsia and are not found to have a peptic ulcer by X-ray or endoscopic examination are classified as ‘non-ulcer’ or ‘functional’ dyspepsia” [2]. More precisely, functional dyspepsia (FD) is defined as dyspepsia

without any known organic etiology such as PUD including scars, erosive gastritis or upper GI malignancies [3].

In other words, if there is no crater, there is no PUD, and patients with symptoms but no crater are said to have ‘functional dyspepsia’, while those with a crater but no symptoms are said to have ‘asymptomatic PUD’ (see Table 1).

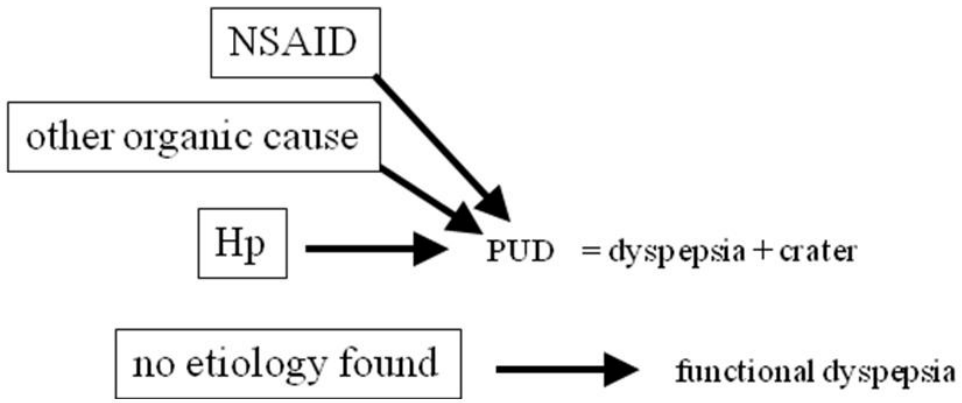
Table 1: Dyspepsia versus crater

	dyspepsia	no dyspepsia
crater	PUD	asymptomatic PUD
no crater (or other cause)	'functional' dyspepsia	healthy

However, Table 1 conceals disconcerting data. There is a poor correlation between active ulcers and symptoms of dyspepsia, since there is still endoscopic evidence of an ulcer in 15% to 40% of duodenal ulcer (DU) patients who become free of symptoms [4]. Conversely, endoscopy shows healed ulcers in many patients who still report symptoms [5], with these patients frequently being categorized as having 'functional dyspepsia' rather than PUD [3]. This begs the question of how many ulcer patients with long-standing symptoms really have symptoms *because of* their ulcer. Linking PUD to the presence or absence of an active crater may be good for the success rate of PUD therapy, but may not be good for the patient.

Complicating things further, there is an often arbitrary distinction between erosion and ulcers in clinical trials [6]. The resulting landscape is shown in Figure 1.

Figure 1: Current causal landscape of PUD



The worldwide prevalence of FD is between 7% and 45%, with large geographic variations [7]. For patients with an ulcer, there is no reason to suppose the prevalence of FD is any lower, unless one says artificially that the symptoms of FD become the symptoms of PUD, and not of FD, at the moment a crater forms.

Excessive acid secretion only occurs in a small proportion of FD patients, and so this cannot be the main cause of FD [8], despite the fact that FD is relieved rapidly by antacids [9]. One can explain this by comparing FD to other chronic functional pain syndromes, where there is often no organic cause and hypersensitivity is suspected to play a major role [10][11]. Here, pain is not caused at the periphery, but instead arises centrally within the brain, when sensory inputs that others might even find pleasurable are interpreted as pain. One familiar example of this is spicy food, which many find enjoyable even if it is physiologically painful. Similarly, FD patients may be more sensitive to acid fluctuations, inflammation and ulcers, and therefore antacids do relieve their symptoms temporarily, even if their acid levels do not differ significantly from those of healthy individuals. In fact, acid reducers might actually trigger compensation mechanisms in FD patients, so that their sensitivity increases over time.

Treatment of FD leads to equivocal results, and high placebo response rates make any interpretation difficult. When FD patients are followed up for 5 to 7 years, 50% show benign but recurrent disease [7]. Clearly, focusing on dyspepsia symptoms ‘caused by an ulcer’, rather than on the ulcer itself, leads to quite a different picture.

Psyche lost, psyche regained

PUD used to be cited as a prime example of a psychosomatic disorder. According to this view, put forward by F. Alexander in the 1940s and 1950s, there were a limited number of such disorders, each with a distinct emotional pattern [12]. On closer inspection, however, this was rather a mechanistic approach that was not friendly to the psyche. In addition, stress was seen as a largely undifferentiated ‘blob’ (and still is for the most part), and was investigated on this basis. However, when many things with contradictory consequences are put into a single construct in this way, the construct ultimately has no consequences. It is like trying to determine the influence of colors by studying white light – it is only when the colors are broken apart into a spectrum that the study has meaning. This monolithic approach has proven rather sterile for health care providers and for patients.

The situation with PUD has been made worse by the fact that psychology and microbiology researchers tend to have little interest in each other's domain [13]. The cause of PUD is now seen as purely microbial, as opposed to psychological, with the Helicobacter pylori (Hp) literature tending to describe therapy simply as the eradication of Hp. It assumes that the Hp infection *is* the disease, and therefore it is similar to, for example, bacterial pneumonia.

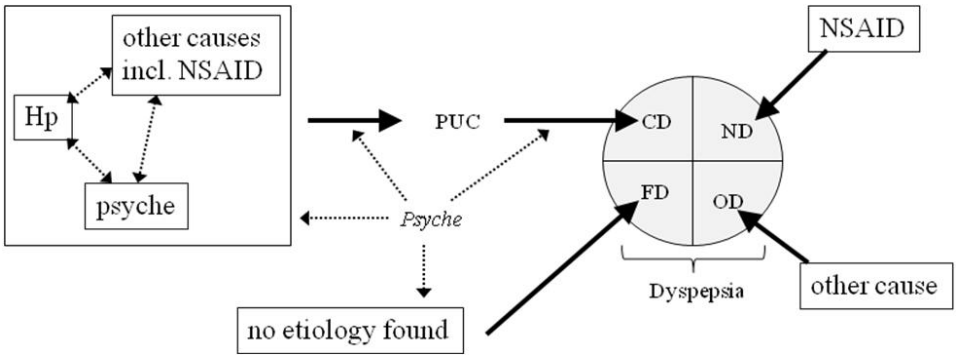
Despite this, the influence of the psyche on gastrointestinal function and symptoms, including gastric discomfort and dyspepsia under stress, are universal human experiences [14]. Furthermore, the influence of stress on dyspepsia has been well documented scientifically, as have its many other effects, including those on gastrointestinal tract function, brain/gut interactions in IBS, inflammatory bowel disease, food antigen responses and gastroesophageal reflux disease (GERD) [15]. Aside from increased visceral awareness, the effects can arise physiologically through alterations in intestinal motility (according to Holtmann et al., this is most affected by impulsivity [16]), secretion and permeability, as well as through negative effects on mucosal regenerative capacity, mucosal blood flow and intestinal microbiota. Additionally, mast cells may release a wide range of neurotransmitters and proinflammatory cytokines under psychological influence, 'fuelling the fire' [17][15].

Since Hp is difficult to detect (luck was needed to detect it originally), it is theoretically possible that some Hp infests every untreated stomach asymptomatically. This would explain why duodenal ulcers are less infected with Hp initially [18]. Furthermore, individuals who develop PUD do so after decades of Hp infestation, since gastric colonization occurs before the age of 10 in most cases [19]. This leads to a huge question that needs to be answered: Why do so many people with Hp infestations only develop PUD after many years or not at all? This situation can be compared to that with Mycobacterium tuberculosis, which can also reside in the human body for decades until something disturbs the bacteria/host equilibrium [20]. It is also known that psychosocial factors can influence susceptibility to many infections, from the common cold [21] to the development of AIDS [22][23].

As noted previously, it is interesting that dyspepsia is comparable to chronic pain, being an *interpretation* in the mind of what is happening in the body. As with any feeling, it is influenced at the subconceptual level by many affective and cognitive factors before it is conceptualized and felt consciously, with this process including visible signs such as vomiting. Therefore, all forms of dyspepsia are related to the

psyche. Furthermore, since the ulcer may not be the most important manifestation in most PUD cases [24], this puts the psyche completely back into the picture. Figure 2 shows a possible new landscape that takes this into account.

Figure 2 : Alternative psychogenic landscape



*peptic ulcerative crater (PUC); crater-induced dyspepsia (CD); otherwise caused dyspepsia (OD), functional dyspepsia (FD)*F

In the box at the left, psychosocial factors can increase the chance of an Hp infestation turning into an Hp infection. The factors can also increase the likelihood of chronic pain and thus associated NSAID use. The psyche, Hp and NSAIDs can all change the gastric environment and make it more susceptible to other influences. In general, in the same way that the psyche is difficult to control for confounding factors, so are other factors difficult to control for the confounding effects of the psyche.

Geographical prevalence, temporal relationships and Hp-negative DU patients, as well as physiological, immunological and behavioral studies in animals are all evidence against Hp being the cause of PUD [25]. It is most likely that Hp plays an opportunistic role when gastroduodenal mucosal defenses have already been compromised by many other possible factors [26]. The causal correlation between Hp infection and PUD may thus be a vicious cycle or, in combination with other factors, a self-enhancing pattern with Hp as one element. Therefore, healing or lack of recurrence of PUD following the eradication of Hp does not disprove the hypothesis that psychosocial factors play a major role in many cases.

Conclusion

Present-day medicine prefers somatic causes over psychological ones, and thus it tends to explain things systematically in terms of the body. This is the case with PUD, where the bacterium presides at present over the psyche, as does the crater over the symptoms. However, there are many arguments as to why the psyche should be cast in a prominent role on the PUD causal stage. Indeed, this may be an example of what needs to be done in many other medical domains.

References

1. Lewin J, Lewis S. Organic and psychosocial risk factors for duodenal ulcer. *J Psychosom Res* 1995;39:531-48.

2. Wilson JD, Braunwald AS, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, et al. *Harrison's principles of internal medicine*, 12th ed. New York: McGraw-Hill; 1991:532.

3. Sugano K. Should we still subcategorize helicobacter pylori-associated dyspepsia as functional disease? *J Neurogastroenterol Motil* 2011;**17**:366-371.

4. Soll AH, Isenberg JI. *Duodenal ulcer disease*. *Gastrointestinal disease: pathophysiology, diagnosis, management*. 1983 Philadelphia WB Saunders:625-672.

5. Soll AH. *Peptic ulcer and its complications*. *Sleisenger and Fordtran's gastrointestinal and liver disease pathophysiology, diagnosis, management*. 1998 Philadelphia WB Saunders: 620–678.

6. Yeomans ND, Neasdal J. Systematic review: ulcer definition in NSAID ulcer prevention trials. *Aliment Pharmacol Ther* 2008;**27**:465-472.

7. Buzás GM. *Functional dyspepsia: the past, the present and the Rome III classification. Orv Hetil* 2007;**148**:1573-1579.

8. Yeomans ND. The ulcer sleuths: the search for the cause of peptic ulcers. *J Gastroenterol Hepatol* 2011;**26**(Suppl 5):S35-S41.

9. McGuigan JE. Peptic ulcer and gastritis. *Harrison's principles of internal medicine, 12th ed.* 1991 New York McGraw-Hill:1229 1248.

10. Turk DC. Understanding pain sufferers: the role of cognitive processes. *Spine J*. 2004;**4**:1-7.

11. Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: a population study. *Pain* 2006;**123**:19-27.

12. French TM. Franz Alexander, M.D 1891-1964. *Psychosom Med* 1964;**26**:203-206.

13. Levenstein S. Stress and peptic ulcer: life beyond Helicobacter. *BMJ* 1998;**316**:538-541.

14. Levenstein S. Psychosocial factors in peptic ulcer and inflammatory bowel disease. *J Consult Clin Psychol* 2002;**70**:739-750.

15. Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *J Physiol Pharmacol* 2011;**62**:591-599.

16. Holtmann G, Singer MV, Kriebel R, Stacker KH, Goebell H. Differential effects of acute mental stress on interdigestive secretion of gastric acid, pancreatic enzymes, and gastroduodenal motility. *Dig Dis Sci* 1989;**34**:1701– 1707.

17. Jones MP. The role of psychosocial factors in peptic ulcer disease: beyond Helicobacter pylori and NSAIDs. *J Psychosom Res* 2006;**60**:407-412.

18. Hobsley M, Tovey FI, Holton J. Precise role of H pylori in duodenal ulceration. *World J Gastroenterol* 2006;**12**:6413-6419.

19. Cover TL, Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology* 2009;**136**:1863-1873.

20. Levenstein S. The very model of a modern etiology: a biopsychosocial view of peptic ulcer. *Psychosom Med* 2000;**62**:176-185.

21. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med* 1991;**325**:606-612.

22. Leserman J. Role of depression, stress, and trauma in HIV disease progression. *Psychosom Med* 2008;**70**:539-545.

23. Leserman J, Petitto JM, Gu H, Gaynes BN, Barroso J, Golden RN, et al. Progression to AIDS, a clinical AIDS condition and mortality: psychosocial and physiological predictors. *Psychol Med* 2002;**32**:1059-1073.

24. Spiro H. Peptic ulcer is not a disease, only a sign! Stress is a factor in more than a few dyspeptics. *Psychosom Med* 2000; **62**:186-187.

25. Hobsley M, Tovey FI, Holton J. Controversies in the helicobacter pylori/duodenal ulcer story. *Trans R Soc Trop Med Hyg*. 2008;**102**:1171-1175.

26. Weiner H. Reductionism once again. The example of helicobacter pylori. *Psychother Psychosom Med Psychol* 1998;**48**:425-429.

The choked heart and how to release it

This article examines how our difficulty in seeing how the mind influences the body, and how this can make us blind to the possibility of 'symptoms' actually being part of the cause. Even in a domain as important as myocardial ischemia, the accompanying strangling or choking sensation is a case in point – with potential life-or-death consequences for many sufferers. In cardiology too – the science of the heart – it is important not to neglect matters of the heart.

4.15 FULL ARTICLE: The choked heart and how to release it

> "A strong man who, having received an injury and affront from one more powerful than himself, and upon whom he could not have his revenge, was so overcome with hatred and spite and passion, which he yet communicated to no one, that at last he fell into a strange distemper, suffering from extreme oppression and pain of the heart and breast…" (W.Harvey, 1628) [1]

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Abstract

After a short enumeration of psychosocial influences on the heart, we examine the possible influence of the psyche on coronaries in cases of angina pectoris and acute myocardial infarction. We hypothesize that the feeling of oppression which is frequently noted by these patients is not the consequence of the ischemia itself, but is instead the consequence of its underlying cause, or even part of this cause itself. This is first and foremost a mental pattern of 'oppression'. Evidence for this comes from clinical as well as epidemiological studies. We see the pathophysiological mechanism being coronary vasospasm, which may be involved in ischemia more frequently than is nowadays thought, and we explain the possible link between psyche and body that gives rise to this. Furthermore, we hypothesize that this knowledge can be applied practically through *coronary opening imagery*, which, in conjunction with established therapeutic approaches, could save lives. Such a mental imaging approach would be easy for patients to learn, and could be used preventively (preferably) or in cases of acute need.

Main Text

THE HYPOTHESIS

"A *feeling of strangling oppression* – tightness, heaviness and related sensations – is a frequent characteristic of pain during acute myocardial ischemia episodes. However, this feeling is not a consequence of ischemia, but instead is a consequence of – or even part of – the underlying cause, mostly transient coronary vasospasm. Furthermore, if a mental pattern can induce coronary vasospasm, then in principle it can also prevent it. Therefore, it follows directly that the use of *coronary opening imagery* during episodes of acute myocardial ischemia may provide a novel therapy."

Under this hypothesis, the pain itself may be caused by ischemia. However, it is felt as painful *oppression* because of a psychosocial oppression pattern, which first translates into a subconscious or partly conscious oppression pattern, and then into a physical realization. Such a *subconscious pattern* can be thought of as a subconceptual neuronal network pattern, as per parallel distributed processing theory [2]. The feeling of oppression may be causally related in several ways, including through a causal chain or through a self-perpetuating pattern [3].

IMPORTANCE

In the US, coronary heart disease accounts for approximately 21% of deaths. About 1,200,000 people in the US have an acute myocardial infarction (AMI) each year, of which 40% die [4]. It is the leading cause of death in people aged less than 75 years [5][6]. Between 20% and 40% of sudden cardiac deaths are precipitated by acute emotional stressors (notably anger-like stress) [7].

Eight million patients visit US emergency departments each year due to chest pain. [8]. Many of these patients are not satisfied when physicians first exclude potentially lethal causes and then provide no further treatment. Understandably, these patients also want pain relief, leading to a high number of costly readmissions [8]. Presently, the mainstay of pain control in acute myocardial ischemia is morphine and nitroglycerine, which provokes both respiratory depression and hypotension

[9]. Thus, *coronary opening imagery* may be a welcome addition to treatment. In addition to its 'de-strangling' effect, it may provide profound mental relaxation during an AMI episode, reducing catecholamine levels, decreasing coronary vascular resistance, inhibiting platelet aggregation, and raising the ventricular fibrillation threshold.

Coronary opening imagery in conjunction with first-line therapy may also be a very cost-effective way of reducing the number of percutaneous coronary interventions (PCI) used to treat stable angina. The 2007 COURAGE study of 2287 volunteers with stable angina pectoris compared two groups, both of which received optimal care (medication, physical exercise, and advice to quit smoking). However, one group received additional PCI and a stent, whereas the other group did not. Both groups had the same levels of myocardial ischemia and general mortality [10], and there was only a modest difference in chest pain relief [11]. Less than 10% of the patients who received PCI reported almost complete pain relief after a year – and that number diminished subsequently [12]. Given the typically diffuse nature of coronary artery disease and the fact that PCI only treats a segment of a coronary artery, this is not surprising. "Optimal medical therapy should be routine first-line therapy, with PCI reserved for patients with severe baseline angina or symptoms unresponsive to medical therapy." [13]

THE 'STRANGLE'

Etymology: *Angina, noun. [Latin expression, from angere to strangle, to choke. See Anger, noun.].* Webster's Online Dictionary

Other terms that people with myocardial ischemia use to describe their chest pain and which denote a severe constriction include: heaviness, pressure, fullness, squeezing, tightness, heavy weight, spasms, crushing, cramping and oppressing.

Angina pain is often felt in the chest, but may spread to arms, shoulders, neck, jaw, back or epigastrium. This is due to referred pain, and, unlike chest pain, is generally not oppressive.

PSYCHOCARDIOLOGY AND MYOCARDIAL ISCHEMIA

Folk wisdom has closely linked psyche and heart over the ages, and modern science follows in these footsteps. For instance, due to arrhythmias, psychosocial stress significantly increases the risk of sudden cardiac death [14][15]. There is also much evidence that the brain cortex, brain stem and ANS directly affect arrhythmogenic mechanisms [1]. In yet another example, a study by [16] supported the concept of negative affect as a common pathway shared by depression, anxiety, anger, and impairments to autonomic cardiac function [16].

Ischemic heart disease (IHD) studies have shown that psychosocial stress is important in all stages of the disease, from traditional atherosclerosis risk factors through to plaque rupture, thrombosis and ensuing lethal arrhythmias [17]. Half of the patients who experience an AMI have low cardiovascular risk profiles [18] which may also point to the importance of psychosocial factors.

The psyche influences chronic hypertension, both causally [19][20][21] and therapeutically [22][23][24][25][26][27]. Similar influences have been seen on cholesterolemia [28], although this remains more controversial. Atherosclerosis, including that of the coronary arteries, is correlated with chronic stress and emotional factors such as strong anxiety and anger [14][18][29][30]. Well-documented pathways for this are the HPA axis and chronic inflammation [18], and a heightening of cortisol levels and blood coagulation [30][31].

Aside from this, acute stress also triggers heart ischemia (both angina pectoris and AMI) [30], including in individuals under 40 years of age [32]. It seems to be particularly fatal in combination with suppressed anger [33]. The INTERHEART study, with over 16.000 participants from 52 countries, showed that psychosocial stress is responsible for approximately 30% of known AMI risk [34]. Its recognized influence is at least as large as that of high blood pressure or hypercholesterolemia [30].

Epidemiologically, there is a correlation between depression and the risk of myocardial ischemia, heightened mortality, and complications from acute heart pathology [35][36][37][38][39][40][41][42][43].

Emotional factors trigger acute cardiac events in patients with advanced atherosclerosis [5]. There is population-based evidence for this, such as hospital admissions for acute coronary syndrome (ACS) after earthquakes, sporting events and terrorist incidents. There is also individual evidence: ACS survivor interviews

show that anger and stress (created by situations such as high-pressure deadlines or driving in traffic) can trigger ACS within a few hours in vulnerable individuals, as can depression, with odds ranging from 2.5 to 4 [5]. Sports spectators experience cardiovascular events more frequently following a loss, and especially a home loss [44]. Other emotional triggers of AMI include Mondays, winter, emotional upset, overeating, lack of sleep, cocaine, sex, Christmas and New Year [45]. Generally, 18% of AMI patients report that emotional upset preceded the AMI itself [46]. However, this rather low number does not include emotional factors that are not *consciously* perceived, such as suppressed anger, and therefore may be a substantial underestimation.

Thus, in accordance with our hypothesis, psychosocial circumstances that trigger angina pectoris and AMI frequently have a 'choking' component, such as anger or the pressure of a deadline. Even general distress is not an amorphous entity to be captured in a single score, but is pattern-related. It is a sense of negative imbalance between 'what should be' and 'what can be', making a person feel trapped, strangled by their burden and inability to cope.

As is well known, stress can lead to symptoms throughout the body due to constriction of muscles and arteries, with coronary vasoconstriction just being an example of this. This indicates a general need to open up or 'contextualize' [47] the concept of stress, and to research pattern-related influences on health and disease.

On the first day of Iraqi missile strikes in Israel, there was a 58% increase in mortality, which was largely attributable to AMI and sudden cardiac death [48]. However this was not seen in later attacks [45]. The wearing of gas masks and associated sense of 'suffocation' is suspected of contributing to this situation [45]. Surprisingly, there was no increase in cardiac deaths during the 9/11 attacks in New York [5], perhaps due to the absence of a continued feeling of personal threat following the initial disastrous events.

In a study by Denollet et al. (N=87, with MI follow-up after 6-10 years), the estimated risk of new cardiac events (cardiac deaths or nonfatal MIs) was 4.7 times larger with distressed personality type D, a homogeneous subgroup exhibiting social inhibition and a tendency to suppress negative emotions. The mechanisms for this are not well understood [49]. However, as per our hypothesis, these people may naturally be more susceptible to the 'choking' nature of their circumstances.

Phobic anxiety, obviously another 'choking' circumstance, is associated with fatal IHD [50], with the association remaining evident during at least the first 10 years of follow up [51].

In general, psychosocial factors are difficult to investigate scientifically, which leads to a bias towards the 'tangible' in research. However, the reality may well be that there are even more psychosocial influences on somatic 'matters of the heart'.

CARDIAC SYNDROME X

This is a 'typical' chest pain without recognizable accompanying myocardial ischemia.

In early reports, 30% of patients undergoing coronary arteriography for chest pain had a normal coronary arteriogram [52], with the numbers being somewhat lower in later studies, probably due to a stricter definition of 'normal'. These patients were labelled as having 'syndrome X' (not to be confused with metabolic syndrome X). More recent studies have also shown that syndrome X is not associated with significant myocardial ischemia or reduction in regional contractility. According to a study by Rosen et al., syndrome X cases seem to involve abnormal central processing of afferent pain messages from the heart [53]. In addition, Pasceri et al. showed that patients with syndrome X have pain hypersensitivity [54], which is a common finding in functional pain syndromes.

Conversely, Holter monitoring shows that up to 70% of myocardial ischemia episodes in CAD patients may be asymptomatic [4], as 30% may be in AMI (*silent ischemia*) [55].

There is a wider implication here. If chest pain is possible without myocardial ischemia and vice versa, what about cases of 'painful myocardial ischemia'? Is the chest pain caused by the ischemia or, for example, are they related instead through a shared common cause?

This leads to the following diagram showing the possible intersections between myocardial ischemia and chest pain:

	myocardial ischemia	**no myocardial ischemia**

'typical' chest pain	?	syndrome X
no chest pain	silent ischemia	normal

In cases of 'painful myocardial ischemia', there is no certainty about how things are related, causally or otherwise, and to what degree. In addition, there may be a vicious circle involved: chest pain may heighten the feeling of oppression which in turn heightens the chest pain. A kindling mechanism may even reinforce this pattern in case of recurring angina pectoris, eventually leading to AMI.

CORONARY ARTERY SPASM

Coronary constriction is a normal phenomenon, and is not necessarily a pathological one. The degree of constriction may vary considerably between patients, as well as within the same patient. Coronary artery spasm (CAS) can occur in both large and small coronary arteries [56], and can, at its most extreme, result in hyperconstriction involving the entire coronary artery and total occlusion. It may be so severe that myocardial ischemia can occur with coronary arteries that are angiographically normal [57]. Prinzmetal et al. described CAS-related angina in 1959 as such a variant form of angina pectoris [58].

Some claim that more than 80% of AMI cases are the result of coronary atherosclerosis with superimposed luminal thrombus [59]. However, coronary artery spasm (CAS) appears to play an important role in the pathogenesis of AMI and other IHD (including effort angina, unstable angina and sudden cardiac death), with or without significant coronary stenosis [57][60][61][62][63][64]. Smoking and low-grade inflammation may be important risk factors of CAS, but precise mechanisms remain largely unknown [56]. CAS occurs more frequently in the early morning, as does any form of IHD [57], which may be related to feeling the pressure of the coming day.

The prevalence of CAS is deemed to be low but is probably underestimated, especially in cases of atherosclerotic coronary lesions [65]. CAS without

atherosclerosis appears to be more common in Japan and Korea, occurring most often between from midnight and early morning [57]. In Japan, epicardial coronary artery vasospasm has been described as *tako-tsubo syndrome*, which presents as acute angina pectoris with life-threatening complications during its acute phase. It accounts for a significant proportion of patients with acute coronary syndrome, with the most common trigger being severe emotional stress, such as tension, anger or anxiety [66][67]. Another name for it is *broken heart syndrome*.

The relation between CAS and coronary atherosclerosis is probably very complex. CAS may heighten thrombin generation, triggering coronary thrombosis [57], while CAS *with or without* secondary thrombus formation may result in myocardial necrosis [45]. AMI may be caused by a ruptured plaque together with vasospasm, but the vasospasm may disappear shortly afterwards, leaving the remaining atherosclerotic plaque as the apparent culprit. In one study, angiography after AMI was compared to additional angiography within 9 months after the AMI. 1/5 of patients went from lesions that were greater than 50% of minimal luminal diameter to less than 50% (thus prompting unnecessary PCI in a number of patients), probably due to vasoconstriction at the time of infarction [68]. Coronary vasoconstriction may of course also promote plaque rupture, especially when it is recurring.

CAS is difficult to examine systematically with coronary angiography, which may be a reason for the current disinterest of many cardiologists [57]. In one study of 179 patients with CAS, 70% had normal or nearly normal coronary arteries [69], with 52% of these patients showing multi-vessel spasm. In one study of 304 patients with stable angina, 47% had angiographically normal or near normal (less than 20% diameter reduction) coronary arteries. In 62% of these patients, acetylcholine testing provoked epicardial or microvascular coronary spasm [70], suggesting that abnormal coronary vasomotion plays a pathogenic role in this setting.

CAN WE PURPOSELY CONTROL OUR CORONARY ARTERIES?

Most people have no direct conscious control of their cardiovascular system – one cannot simply ‘decide’ to have a heightened blood pressure or heart rhythm. However, there are situations that clearly show the influence of the psyche. For instance, many people find it easy to imagine themselves in a dangerous or stressed

situation, thereby raising their blood pressure and heart rhythm, or to imagine themselves in a relaxed situation, leading to the opposite results. As another example, embarrassment – a psychosocial phenomenon – makes some people turn red in the face, whereas others turn white. Tibetan monks appear to have even more cardiovascular control, and to be able to exercise such control at will. An erection is another very common phenomenon that is both related to the circulatory system and highly psychogenic. Hypnosis has been used effectively to raise skin temperature on selected parts of the body, such as the palm, which can only be accomplished through local vasodilatation [71]. Sudden unexpected death (such as sudden infant death syndrome, voodoo death, death in association with drug abuse, or during grief, major loss or panic attacks) is now recognized as a medical problem of major epidemiologic importance. In many cases, it has been attributed to neural influences on cardiac function, resulting in acute myocardial infarctions and lethal arrhythmias [72]. This has also been related to Curt Richter's experiments from 1957, where wild rats placed in a 'no escape' situation experienced sudden death (they had to swim under high restraint in a glass swimming jar, with their whiskers trimmed) [72].

Or course, the brain can and does permanently regulate blood pressure, heart rate, and peripheral arterial resistance – as well as coronary diameter. Therefore, there is no question about the theoretical *possibility* of our hypothesis. Furthermore, taking erection as an example, one cannot make a purely conscious decision to have an erection or, for that matter, experience psychogenic erectile dysfunction. However, one can achieve an erection through proper use of pattern-related visualization after making a conscious decision to be open to an erection.

Therefore from a *broad* mental viewpoint, one can purposely control one's blood vessels. We hypothesize that this can be extrapolated to coronary arteries. If this is so, then it may lead towards very useful additional therapeutic measures.

A crucial question is whether our brain/mind can subconsciously and at the same time purposely exert control over the body. A significant amount of recent cognitive neuroscience research shows that our subconscious is much more 'decisive' in many areas than previously thought [73]. Even with 'conscious' movement, the movement that immediately follows our decision to move is automatic. There is no decision made between thinking about moving and the act itself. In truth, many decisions that we regard as 'conscious' are decided at the subconscious level *before* they reach consciousness [74]. John-Dylan Haynes has shown in a number of ingenious

experiments that what appears to be a conscious decision can be traced seconds before within the brain [75].

Viewing the brain as a subconceptual pattern-processing device [76], one can see how subconceptual (subconscious) patterns cause, for instance, an erection as well as the conscious decision to have an erection. However, the conscious decision itself is *not* sufficient to achieve the erection. Likewise, it may be that subconceptual pattern-processing leads to both a choked heart and a conscious feeling of oppression. Continuing this line of reasoning, we hypothesize that patients can 'unchoke' their heart through the use of appropriate subconceptual patterns. These subconceptual patterns may also diminish their conscious feeling of oppression, but this diminution does not directly influence their heart (see Figure 1).

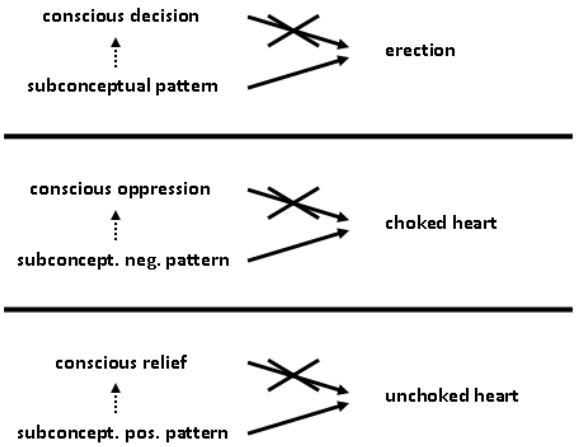

Figure 1: From subconceptual pattern to unchoked heart.

CORONARY OPENING IMAGERY

In the examples of blushing and erection, mental imagery provokes a bodily response over which we have no direct conscious control. Therefore, mental imagery may also be useful in controlling other vascular phenomena, in this case

relieving coronary vasoconstriction. At first glance, mental imagery might be used in patients with recurring angina pectoris but no discernible coronary pathology on coronarography, but it could also be worthwhile even when coronary atherosclerosis is discernible and possibly contributing to the ischemia.

We have developed two scripts and recorded them as sessions that can be used for this purpose. One is for the acute phase, whereas the other is intended for use when symptoms are subsiding. The sessions are available on request (email to jean.luc.mommaerts@pandora.be) and are offered free of charge. They can be used 'live' when someone recognizes a situation of mental oppression or when they start to experience chest pain, but it is advisable for the patient to rehearse the sessions beforehand. Additionally, practicing these in situations where they are needed provides immediate feedback as to whether they are being used effectively. Of course, these should in no way be used in place of normal medical care, nor should patients delay seeking help while they use these sessions.

In order to test our hypothesis, we envision a limited study in an at-risk population. A number of these patients are given access to the sessions and are helped to rehearse them until they are able to use them easily when a relevant situation arises. Of course, many of the results will remain subjective and difficult to evaluate, and a double-blind protocol would not be possible. As an additional possibility, the sessions could be performed by patients during coronary angiography. If many people have access to the sessions, a larger cohort study would be possible, taking into account who has simple access to the sessions and who has rehearsed them well.

CONCLUSION

We hypothesize that subconceptual mental patterns play a substantial role in engendering myocardial ischemia. This is in accordance with the age-old intuition that one can suffer profoundly or even die from extreme oppression of the heart. At the same time, modern research shows how the link between the psyche and the body can be conceptualized. If this hypothesis is correct, then making use of mental patterns through appropriate visualization may be an easy approach that can save many lives. If so, this should be in the first-aid kit of every person over 50 years of age or with special risk factors. Furthermore, if it is correct, this shows the importance of preventively eliminating 'no escape' situations from the environment.

At present, this is common sense, but with scientific background, this can become the norm and a basic human right.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest in this manuscript of any kind, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. Furthermore, there are no sources of funding for this manuscript.

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References

1. Taggart P, Critchley H, Lambiase PD. **Heart-brain interactions in cardiac arrhythmia**. *Heart*. 2011;97:698–708
2. Rumelhart DE, McClelland JL. **Parallel distributed processing: explorations in the microstructure of cognition.** Cambridge, Mass: MIT Press; 1986
3. Mommaerts JL, Devroey D. **Causal Thinking in Psychosomatics, with Peptic Ulcer as Case**. *J Med Philos*. 2013 (in print)
4. American Heart Association. **Heart attack and angina statistics**. American Heart Association:2003.
5. Steptoe A, Brydon L. **Emotional triggering of cardiac events**. *Neurosci Biobehav Rev*. 2009;33:63–70
6. World Health Organization. **The world health report 2004 - changing history.** Geneva: World Health Organization; 2004
7. Vlastelica M. **Emotional stress as a trigger in sudden cardiac death**. *Psychiatr Danub*. 2008;20:411–414
8. Kirk JD, Amsterdam EA. **Use of benzodiazepines for chest pain: a new indication for an old drug?** *J Emerg Med*. 2003;25:459-461

9. Huffman JC, Stern TA. **The use of benzodiazepines in the treatment of chest pain: a review of the literature**. *J Emerg Med*. 2003;25:427–437

10. Prasad A, Rihal C, Holmes DR. **The COURAGE trial in perspective**. *Catheter Cardiovasc Interv*. 2008;72:54–59

11. No authors listed. **'President and Fellows of Harvard College' COURAGE to make choices. When it comes to treating angina or a narrowed coronary artery, angioplasty is no better than medical therapy for preventing heart attacks or premature death.** *Harv Heart Lett*. 2007;17:5

12. Gibbons RJ. **Based upon the results of the COURAGE clinical trial, what is the best treatment for stable angina? Interview by George D. Lundberg.** *MedGenMed*. 2007;9:49

13. Maron DJ. **Using COURAGE to treat angina**. *Medscape J Med*. 2008;10:286

14. Pignalberi C, Ricci R, Santini M. **[Psychological stress and sudden death].** *Ital Heart J Suppl*. 2002;3:1011–1021

15. Brunckhorst CB, Holzmeister J, Scharf C, Binggeli C, Duru F. **[Stress, depression and cardiac arrhythmias]**. *Ther Umsch*. 2003;60:673–681

16. Bleil ME, Gianaros PJ, Jennings JR, Flory JD, Manuck SB. **Trait negative affect: toward an integrated model of understanding psychological risk for impairment in cardiac autonomic function**. *Psychosom Med*. 2008;70:328–337

17. Burg MM, Graeber B, Vashist A, et al. **Noninvasive detection of risk for emotion-provoked myocardial ischemia**. *Psychosom Med*. 2009;71:14–20

18. Alboni P, Alboni M. **[Psychosocial factors as predictors of atherosclerosis and cardiovascular events: contribution from animal models]**. *G Ital Cardiol (Rome)*. 2006;7:747–753

19. Pickering TG, Clemow L. **Paroxysmal hypertension: the role of stress and psychological factors**. *J Clin Hypertens (Greenwich)*. 2008;10:575–581

20. Esler M, Eikelis N, Schlaich M, et al. **Chronic mental stress is a cause of essential hypertension: presence of biological markers of stress**. *Clin Exp Pharmacol Physiol*. 2008;35:498–502

21. Gleiberman L. **Repressive/defensive coping, blood pressure, and cardiovascular rehabilitation**. *Curr Hypertens Rep*. 2007;9:7–12

22. Schwickert M, Langhorst J, Paul A, Michalsen A, Dobos GJ. **[Stress management in the treatment of essential arterial hypertension]**. *MMW Fortschr Med*. 2006;148:40–42

23. Abgrall-Barbry G, Consoli SM. **[Psychological approaches in hypertension management].** *Presse Med*. 2006;35:1088–1094

24. Rainforth MV, Schneider RH, Nidich SI, Gaylord-King C, Salerno JW, Anderson JW. **Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis.** *Curr Hypertens Rep*. 2007;9:520–528

25. Walton KG, Schneider RH, Nidich SI, Salerno JW, Nordstrom CK, Bairey Merz CN. **Psychosocial stress and cardiovascular disease Part 2: effectiveness of the Transcendental Meditation program in treatment and prevention**. *Behav Med*. 2002;28:106–123

26. Frumkin K, Nathan RJ, Prout MF, Cohen MC. **Nonpharmacologic control of essential hypertension in man: a critical review of the experimental literature**. *Psychosom Med*. 1978;40:294–320

27. Linden W, Moseley JV. **The efficacy of behavioral treatments for hypertension**. *Appl Psychophysiol Biofeedback*. 2006;31:51–63

28. Calderon R, Schneider RH, Alexander CN, Myers HF, Nidich SI, Haney C. **Stress, stress reduction and hypercholesterolemia in African Americans: a review**. *Ethn Dis*. 1999;9:451–462

29. Vale S. **Psychosocial stress and cardiovascular diseases.** *Postgrad Med J*. 2005;81:429–435

30. Rozanski A, Blumenthal JA, Kaplan J. **Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy**. *Circulation*. 1999;99:2192–2217

31. Nemeroff CB, Musselman DL. **Are platelets the link between depression and ischemic heart disease?** *Am Heart J*. 2000;140(Supp 1):57–62

32. Sengül C, Ozveren O, Cevik C, et al. **[Comparison of psychosocial risk factors between patients who experience acute myocardial infarction before and after 40 years of age]**. *Turk Kardiyol Dern Ars*. 2011;39:396–402

33. Mittleman MA, Maclure M, Sherwood JB, et al. **Triggering of acute myocardial infarction onset by episodes of anger. Determinants of myocardial infarction onset studyiInvestigators**. *Circulation*. 1995;92:1720–1725

34. Das S, O'Keefe JH. **Behavioral cardiology: recognizing and addressing the profound impact of psychosocial stress on cardiovascular health.** *Curr Atheroscler Rep*. 2006;8:111–118

35. Follath F. **[Depression, stress and coronary heart disease--epidemiology, prognosis and therapeutic sequelae]**. *Ther Umsch*. 2003;60:697–701

36. Zellweger MJ, Osterwalder RH, Langewitz W, Pfisterer ME. **Coronary artery disease and depression**. *Eur Heart J*. 2004;25:3–9

37. Bounhoure JP, Galinier M, Curnier D, Bousquet M, Bes A. **[Influence of depression on the prognosis of cardiovascular diseases]**. *Bull Acad Natl Med*. 2006;190:1723–1731; discussion 1731–1732

38. Roose SP. **Depression, anxiety, and the cardiovascular system: the psychiatrist's perspective**. *J Clin Psychiatry*. 2001;62(Supp 8):19–22; discussion 23

39. Jiang W. **Impacts of depression and emotional distress on cardiac disease**. *Cleve Clin J Med*. 2008;75(Suppl 2):S20–S25

40. O'Connor CM, Gurbel PA, Serebruany VL. **Depression and ischemic heart disease**. *Am Heart J*. 2000;140(Supp 4):63–69

41. Wu ZS. **[Epidemiological studies on the relationship between psychosocial factors and cardiovascular disease].** *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. 2001;23:73–77,82

42. Plante GE. **Depression and cardiovascular disease: a reciprocal relationship**. *Metabolism*. 2005;54(5 Suppl 1):45–48

43. Todaro JF, Shen BJ, Niaura R, Spiro A 3rd, Ward KD. **Effect of negative emotions on frequency of coronary heart disease (The Normative Aging Study)**. *Am J Cardiol*. 2003;92:901–906

44. Leeka J, Schwartz BG, Kloner RA. **Sporting events affect spectators' cardiovascular mortality: it is not just a game**. *Am J Med*. 2010;123:972–977

45. Kloner RA. **Natural and unnatural triggers of myocardial infarction**. *Prog Cardiovasc Dis*. 2006;48:285–300

46. Tofler GH, Stone PH, Maclure M,, et al. **Analysis of possible triggers of acute myocardial infarction (the MILIS study)**. *Am J Cardiol*. 1990;66:22–27

47. Segerstom S. **The Oxford Handbook of Psychoneuroimmunology**. Oxford: Oxford University Press; 2012;p.XVIII

48. Kark, JD, Goldman, S, Epstein, L. **Iraqi missile attacks on Israel. The association of mortality with a life-threatening stressor**. *JAMA*. 1995;273:1208–1210

49. Denollet J, Brutsaert DL. **Personality, disease severity, and the risk of long-term cardiac events in patients with a decreased ejection fraction after myocardial infarction**. *Circulation*. 1998;97:167–173

50. Kawachi I, Colditz GA, Ascherio A, et al. **Prospective study of phobic anxiety and risk of coronary heart disease in men**. *Circulation*. 1994;89:1992–1997

51. Haines A, Cooper J, Meade TW. **Psychological characteristics and fatal ischaemic heart disease**. *Heart*. 2001;85:385–389

52. Pepine CJ, Balaban RS, Bonow RO, et al. **Women's ischemic syndrome evaluation: current status and future research directions: report of the National Heart, Lung and Blood Institute workshop: October 2-4, 2002: Section 1: diagnosis of stable ischemia and ischemic heart disease**. *Circulation*. 2004;109:e44–46

53. EA Mayer, MC Bushnell editors. Functional pain syndromes. Seattle: IASP Press; 2009

54. Pasceri V, Lanza GA, Buffon A, Montenero AS, Crea F, Maseri A. **Role of abnormal pain sensitivity and behavioral factors in determining chest pain in syndrome X**. *J Am Coll Cardiol*. 1998;31:62–66

55. EA Mayer, MC Bushnell editors. **Functional pain syndromes**. Seattle: IASP Press; 2009. Chap 6

56. Yoo SY, Kim JY. **Recent insights into the mechanisms of vasospastic angina**. *Korean Circ J*. 2009;39:505–511

57. Yasue H, Nakagawa H, Itoh T, Harada E, Mizuno Y. **Coronary artery spasm--clinical features, diagnosis, pathogenesis, and treatment**. *J Cardiol*. 2008;51:2–17

58. Prinzmetal M, Kennamer R, Merlis R, Wada T, Bor N. **Angina pectoris. 1. A variant form of angina pectoris**. *Am J Med.* 1959;27:375–88.

59. Burke AP, Virmani R. **Pathophysiology of acute myocardial infarction**. *Med Clin North Am*. 2007;91:553-572;ix.

60. Stern S, Bayes de Luna A. **Coronary artery spasm: a 2009 update**. *Circulation*. 2009:12;119:2531–2534

61. Hanratty CG, Koyama Y, Rasmussen HH, Nelson GI, Hansen PS, Ward MR. **Exaggeration of nonculprit stenosis severity during acute myocardial infarction: implications for immediate multivessel revascularization**. *J Am Coll Cardiol*. 2002;40:911–916

62. Kimball BP, LiPreti V, Aldridge HE. **Quantitative arteriographic responses to ergonovine provocation in subjects with atypical chest pain**. *Am J Cardiol*. 1989;64:778–782

63. Sugiishi M, Takatsu F. **Cigarette smoking is a major risk factor for coronary spasm**. *Circulation*. 1993;87:76–79

64. Marzilli M, Goldstein S, Trivella MG, Palumbo C, Maseri A. **Some clinical considerations regarding the relation of coronary vasospasm to coronary atherosclerosis: a hypothetical pathogenesis**. *Am J Cardiol*. 1980;45:882–886

65. Halna du Fretay X, Blanchard-Lemoine B, Schnebert B, Viossat J. **[Variant angina: which approach in 2011?]**. *Ann Cardiol Angeiol (Paris)*. 2011;60:317–323

66. Sinning Ch, Keller T, Abegunewardene N, Kreitner KF, Münzel T, Blankenberg S. **Tako-Tsubo syndrome: dying of a broken heart?** *Clin Res Cardiol*. 2010;99:771–780

67. Buchholz S, Rudan G. **Tako-tsubo syndrome on the rise: a review of the current literature**. *Postgrad Med J*. 2007;83:261–264

68. Hanratty CG, Koyama Y, Rasmussen HH, Nelson GI, Hansen PS, Ward MR. **Exaggeration of nonculprit stenosis severity during acute myocardial**

infarction: implications for immediate multivessel revascularization. *J Am Coll Cardiol*. 2002;40:911–916

69. Yasue H, Kugiyama K. **Coronary spasm: clinical features and pathogenesis**. *Intern Med*. 1997;36:760-765

70. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. **High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries)**. *J Am Coll Cardiol*. 2012;59:655–662

71. Hajek P, Jakoubek B, Kyhos K, Radil T. ***Increase in cutaneous temperature induced by hypnotic suggestion of pain***. *Percept Mot Skills*. 1992;74:737–738

72. Samuels MA. **'Voodoo' death revisited: the modern lessons of neurocardiology**. *Cleve Clin J Med*. 2007;74(Supp 1):S8–S16

73. Gazzinaga MS editor. **The Cognitive Neurosciences**. Cambridge: The MIT Press; 2009.

74. Dijksterhuis A. **Het slimme onbewuste**. Netherlands: Bert Bakker; 2007

75. Haynes JD, Rees G. **Predicting the stream of consciousness from activity in human visual cortex**. *Curr Biol*. 2005;15:1301–1307

76. Bechtel W, Abrahamsen A. **Connectionism and the mind: parallel processing, dynamics and evolution in networks**. Oxford: Blackwell ;2002

Subconceptual Processing: Nonspecific Factor of Chronic Pain

This article provides substantiated insights into chronic pain as a single condition with many symptomatic patterns, rather than as a consequence of different somatic disorders. Subconceptual processing is implicated as the nonspecific factor in this area. 'Pain' in reality is always a 'perception of pain', and therefore it should come as no surprise that chronic pain is heavily influenced by many conscious and non-conscious psychological factors. We also see this at play to a huge degree in the characteristics of subconceptual processing.

4.16 FULL ARTICLE: Subconceptual Processing: Nonspecific Factor of Chronic Pain

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Submitted in: “Pain”

Abbreviations in this article

chronic functional pain (CFP); subconceptual processing (SP); Subconceptual Processing Theory (SPT); empirically supported treatment (EST); cognitive behavioral therapy (CBT)

Abstract

In the domain of chronic pain, research increasingly points to meaning-related nonspecific factors that take precedence over specific factors of differentiated disorders. Subconceptual Processing Theory as elaborated in this article provides the missing link between these factors and the brain, thus also a rationale for better understanding the origins and possibly new treatment of chronic pain. According to this theory, the human brain being a vast ‘network of networks’, meaning does not reside in single neurons or in any box-like recipients but in overlapping self-enhancing patterns of ‘sub-conceptual’ neurons becoming activated together. These are material patterns equivalent to what one can also see as mental patterns. Such patterns are being explored by Cognitive Neuroscience in many domains of mental processing, bringing deeper meaning into the picture of ‘hard’ science. In analogy to the nonspecific factor of psychotherapy, Subconceptual Processing Theory is about the ‘nonspecific factor of chronic pain’.

Keywords: chronic pain, cognitive behavior therapy, neurology, placebos, psychology, psychosomatic

Introduction: Subconceptual Processing Theory

The 'law of parsimoniousness' is a basic principle of science: when different phenomena can be rationally explained by a single underlying phenomenon, this phenomenon should be studied in its own right, as this frequently leads to a reduction from the macro-level to the micro-level [1]. For example, the concept of waves allows us to exploit water waves, as well as sound and light waves.

Within the domain of chronic functional pain (CFP), subconceptual processing (SP) is such an underlying phenomenon. Subconceptual processing theory (SPT) deals with highly overlapping neuronal network patterns that, at the level of the patterns themselves, process conceptual information, but whose units only contain subconceptual information. When a critical number of nodes within a single pattern are active simultaneously, then the pattern and the information it contains also becomes activated. At this point, this information may rise to the level of consciousness (but not necessarily). Patterns that are not activated still exist as a potential through the way that nodes are connected. SPT is compatible with parallel distributed processing [2], artificial neural networks (ANN) and neurophysiology. Aside from pain, SP likely underlies such seemingly disparate domains as empathy [3], motivation, the placebo effect [4] and psychosomatics.

'Emergent properties' are properties that systems possess which are not found in their individual components, as exemplified by neur(on)al networks and their constituent neurons. In SPT, 'mind science' is about properties that emerge, whereas 'brain science' is about those things that give rise to this emergence ('emergers'). In the same way that rotation is not caused by a wheel, but is what a wheel does, so mental functions such as pain are not caused by the brain, but are what the brain does at the system level. Nothing resembling pain can be seen within the brain's constituents, and thus pain is an emergent property of the brain.

This provides a solution to the Cartesian problem of how material soma and immaterial psyche can influence each other, and also explains how we can directly and meaningfully influence changes in the body's pain matrix through psychological means. The *pain neuromatrix* as conceived by Melzack and discussed later on in this article is a network of such neuronal networks. Pain 'emerges' when there is a relevant communication of 'change' from the periphery of the body to this network of networks [5]. We are not conscious of the emergers or the process of emergence

except in the last stages, and only then if it is of sufficient importance. The subconceptual processing that occurs before we consciously feel pain takes place in the neur(on)al network, and is influenced by an enormous number of deeply meaningful subconceptual patterns that are a fundamental part of our identity.

Chronic pain is always 'in the head'

According to population-based studies, 20 to 40% of older adults have problems related to chronic pain. In long-term care facilities, up to 83% of residents have at least one problem associated with chronic pain [6]. Around 70% of the 10 million cancer patients who are diagnosed annually suffer from mostly long-lasting cancer pain [7]. Chronic pain is a huge economic issue, with total annual costs in the US estimated at $100 billion [8].

However, it is not easy to give a clear definition of pain that is useful in practice. Meskey, as president of a committee of the International Association for the Study of Pain (IASP) provided the following definition: "*Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage … It is unquestionably a sensation in a part of the body but it is also always unpleasant and therefore also an emotional experience … Many people report pain in the absence of tissue damage or any likely pathophysiological cause. If they regard their experience as pain and if they report it in the same way as pain caused by tissue damage, it should be accepted as pain.*" [5]. McCaffery simply describes pain as "*whatever the experiencing person says it is, existing whenever he or she says it does.*" [9] The more one delves into pain, the more one sees its intrinsically subjective and meaningful nature. In this respect, two modes of 'feeling pain without pain' noted by Descartes are intriguing: "*I could have a constant but mild pain in my hand, and then find I had ceased to 'feel' it for a while due to someone's engaging me in conversation. Secondly, there is the case of phantom-limb pain: I may 'feel a pain in my hand' even if the hand has been amputated.*" [10] In both instances, pain can gradually emerge into consciousness or fade away.

Chronic pain is defined by the IASP as *"… pain which persists past the normal time of healing … With non-malignant pain, 3 months is the most convenient point of division between acute and chronic pain." [*11] However, conventional definitions such as this do not consider pain severity or associated disabilities. Von Korff and

Dunn advocate defining chronic pain using a risk score based upon pain intensity, number of pain sites, pain-related activity limitations, depressive symptoms and days of pain [12]. This has better predictive value for future pain and disability [13] than pain duration alone, although long-term pain outcomes are highly variable and uncertain. Chronic pain is a continuum rather than a distinct entity that defines 'chronic pain patients'. It is much more fluid than acute pain, and usually says little about any underlying disease process. Even so, for many patients and frequently their surroundings as well, it becomes a relentless focus over time, with many elements contributing to the final pain response. In contrast to acute pain, it is often accompanied by depression and anxiety, and appears to be much more related to meaningful patterns than does acute pain. It should therefore be viewed as fundamentally different from the prolonged presence of acute pain. This difference can also be seen in brain imaging. For example, amygdala changes seen with acute pain are very distinct from those of chronic pain [14]. Treatment results (or lack of results) also point in this direction, with treatments that have strong effects on acute pain (such as rest, immobility and opioid analgesics) having limited usefulness for most chronic pain patients [15].

Over the past three to four decades, it has become increasingly clear that chronic pain is related to a myriad of psychosocial factors such as cultural background, past experiences, the meaning of the pain, personality characteristics, arousal level, attention and emotions [16-18]. Considering pain intensity in isolation fails to adequately reflect psychological and physical disruption [19]. For instance, Flor and Turk found that physical factors in patients with lower back pain did not predict severity of pain, interference with normal life, or visits to physicians. In the same population, however, feelings of helplessness and hopelessness were predictive of pain impact self-reporting, as well as of pain response behavior [20].

One can distinguish nociception (processing of stimuli related to the stimulation of nociceptors and experienced as pain); pain (involving conscious awareness of nociception, appraisal and learning, and integration and modulation of afferent and efferent processes) and suffering (including factors associated with pain's impact on the ability to function) [21]. On the other hand, Melzack and Casey saw three major psychological dimensions of pain: 1) sensory-discriminative, 2) motivational-affective and 3) cognitive-evaluative [22]. This division has dominated thinking about pain. However, thought, action and emotion are only strictly separable in theory [23], with any actual pain experience emerging from their dynamic interplay.

In fact, we are barely consciously aware of many factors that modulate pain. People may even subconsciously infer their level of pain by observing their own response to the situation causing pain [24].

Functional imaging techniques show that neural pain structures are very complex, with no single 'pain center'. Many cortical areas can be activated during pain, with wide variation within and between individuals [25]. There are direct spinal inputs to lower brainstem and limbic structures, providing rudimentary aspects of pain affect (arousal and somatomotor activation), as well as spinothalamic pathways to medial thalamic nuclei. Information flows back and forth between a number of brain centers, especially the insula and anterior cingulate cortex (ACC), with no strict allocation of specific pain perception functions (such as sensory versus affective or cognitive) to specific brain regions. For example, the insula is a site for sensory and affective *integration* [26]. All of this is transparent to our conscious awareness, and we consciously experience 'pain' directly because this transparency works. However, this does not mean that processing is devoid of meaning, even if we cannot probe such meaning effectively today. Present investigation methods are very coarse, especially when combining time and space measurements. To have a complete view of meaningful patterns would require simultaneous single-cell recordings across large numbers of cells, which is not feasible with present-day technology.

Recent thinking about pain has focused increasingly on the brain, with Gate Control Theory being developed by Melzack and Wall and physiologically verified over the past four decades. In brief, impulses from small-diameter afferent neurons are influenced by nerve impulses in efferent pathways, opening and closing pain pathways in the spine under the influence of a variety of psychological factors. In the 1980s, Melzack developed Neuromatrix Theory, inspired by data about the phenomenon of phantom limbs located below total spinal sections in paraplegics. These patients can experience almost every aspect of pain sensation and affect (burning, cramping, and so on) in a phantom limb, despite the absence of inputs from the body. To put this succinctly, "*The origins of the patterns that underlie the qualities of experience lie in neural networks in the brain; stimuli may trigger the patterns but do not produce them."* [27] A critical component of the pain neuromatrix approach is that pain is experienced in the body image held by the brain (the 'virtual body') [28].

It is noteworthy that small-diameter afferents detect *changes* in body tissue [28], providing a predominantly 'top-down' view of pain processing. It is well known that top-down processing plays a fundamental role in shaping many kinds of perceptual experiences, including visual, auditory and somatosensory ones [29]. Melzack states that "*Pain is a multidimensional experience produced by characteristic 'neurosignature' patterns of nerve impulses generated by a widely distributed neural network in the brain.*" [27] The neurosignature originates and takes form in the neuromatrix, although it may be triggered or modulated by inputs. The brain is central to pain, whatever its perceived source, with many brain areas at work and a significant amount of meaningful processing apparently taking place. However, by focusing on each brain area individually, we lose track of how meaning is represented. At the other end of this fog, we encounter discrete neurons and synapses which contain no meaning. However, SPT is starting to clear this fog.

When pain becomes chronic, there is an increase and diversification in the ways that the pain neuromatrix can be activated. In addition, there are alterations in the morphology and behavior of the neuromatrix which further alter outputs [28]. For example, systems that regulate stress may produce alterations in nervous tissue, producing neural 'distress' patterns that contribute to the overall neuromatrix [28].

For instance, in the case of low back pain, changes in pain levels caused by body repositioning or other manipulations provide evidence that the end organ is involved [30]. However, brain imaging of patients with lower back pain provides ample evidence of abnormalities in various brain properties that are more tightly correlated to pain intensity and duration than is end-organ pathology [30]. Unfortunately, the effectiveness of treatments based on both models is equally disappointing [30]. The prevailing hypothesis is that "*the etiology of these disorders probably involves a complex interplay between CNS control of peripheral organs and relay of information back to the CNS, as well as the impact of affective disorders on processing of information, and environmental exposures including stress and trauma.*" [31]

In many patients with functional pain syndromes, enhanced pain sensitivity (hyperalgesia and allodynia) is a common and central feature [32-33]. This suggests that pain amplification, as well as the associated processes that mediate pain transmission and modulation, are key factors in maintaining these syndromes [34]. These processes again are tightly related to meaning.

In many patients with functional pain syndromes, what initially seem clear physical causes become less clear over time. In large part, this may be due to the patient's and physician's desire to find more tangible explanations than 'the invisible psyche'. A broadly similar example is chronic lower back pain, which was thought to result mainly from degenerative changes in lumbar intervertebral disks and facet joints. However, it was shown subsequently that such changes are widespread in both symptomatic and asymptomatic individuals, making any statistical correlation between symptoms and structural abnormalities modest at best [30,35-36]. In fact, psychological disorders may play a larger role than thought previously, since about half of patients with chronic lower back pain may also have post-traumatic stress [37].

Functional pain syndromes – many and one

In most cases, when a patient complains of chronic pain and no organic cause is found, they are diagnosed as having one of several 'functional pain syndromes', with the specific diagnosis depending upon location and further symptoms. For example, if abdominal pain is associated with alterations in bowel habits, the diagnosis becomes 'irritable bowel syndrome'. Different labels exist for other organ systems, such as temporomandibular joint disorder, chronic abacterial prostatitis, vulvodynia, functional gall bladder, and so on. If the pain is widespread, possibly due to the spread of an initially localized condition, the diagnosis may become 'fibromyalgia'. This diagnosis through exclusion of organic causes is logical if other possible causes are discrete and non-orthogonal from an organic perspective. However, there is no reason to suppose this is the case. Chronic pain can have simultaneous organic and nonorganic causes. Even with cancer pain, there is a difference between pain intensity and pain affect, the former being mainly organogenic, and the latter mainly functional with affective, cognitive and motivational dimensions playing a substantial role. It is worth noting the clear correlation between anger and cancer pain [38].

A significant amount of research points in the direction of a unifying disease mechanism for functional pain syndromes [39]. SPT completes this, providing the 'missing link' or nonspecific factor that appears to underlie many conditions. Indeed, accumulating evidence shows that, compared to healthy controls, these disorders have high levels of co-morbidity with each other, as well as with other stress-related disorders such as chronic fatigue, disorders of mood and affect, and somatization.

[39-40]. They are also associated with syndromes such as chronic tinnitus, asthma, abnormalities in motor and neuroendocrine function, autonomic imbalance, sleep disturbances [41] and even social exclusion [42]. For example, in a study of the Swedish Twin Registry (N=44.897), a strong association was found between chronic widespread pain ('fibromyalgia') and other pain-related disorders such as irritable bowel syndrome and chronic headaches [43]. Two recent studies found chronic pain rates of approximately 80% in recurrent or refractory major depression [44-45]. The occurrence of anxiety disorders in functional pain syndrome patients may be more than three times that of the general population. Brain imaging shows that the brain areas involved in processing functional pain (such as the ACC and prefrontal cortex) overlap with those involved in stress and post-traumatic stress disorder neural circuitry [46-48]. The concept of hidden depression has resulted in antidepressants being given to CFP patients, which probably act as placebos much as they do in depression cases (where 70% to 75% of the total effect is placebogenic when compared to passive placebos, and even more when compared to active placebos). We posit that something at the subconceptual level may underlie CFP *as well as* depression. This is also compatible with the enormous placebo effect seen in (hidden) depression as well as in chronic pain.

The nonspecific factor view predicts a continuum of normalcy. Indeed, to summarize the overlap between chronic pain syndromes and affective spectrum syndromes [49], *"most functional pain syndromes show a lack of a distinct boundary between the large number of healthy individuals in the general population who have experienced characteristic symptoms transiently, and the population in which characteristic chronic symptoms are present but are not severe enough, or do not interfere with an individual's quality of life sufficiently for this person to seek medical or surgical care. This situation is similar to findings with symptom-based psychiatric diagnoses."* [50]

There is a strong support from the idea that *"symptoms may manifest as different syndromes during the life of a patient … As long as we rely on cross-sectional studies for characterization of the index syndrome and comorbidities and ignore their temporal dimension, we will not understand whether there is a common underlying substrate."* [51] This means that one may 'cure' one syndrome, only to have it appear later as another syndrome which again may be 'cured', perhaps by another physician. Thus, patients may be 'cured' many times without being cured at all.

This calls to mind G.L. Engel's characterization of 'pain-prone patients' who *"repeatedly or chronically suffer from one or another painful disability, sometimes with and sometimes without any recognizable peripheral change … It is an adjustment, a way of adaptation, acquired through psychic experience."* [52] When no cause is found, many health care professionals give these patients a functional label, such as "*… they do not believe that the patient really has anything seriously wrong …*" [39]. At present, each functional pain syndrome is studied as a separate entity by different subspecialist researchers, constraining these syndromes to isolated silos.

Chronic pain and depression are increasingly seen as recurrent or chronic disorders (or disorder spectrums) that are much more difficult to treat than previously assumed. Both are no longer seen as completely distinct from their subclinical forms, nor as strictly distinct from other Axis I disorders and personality disorders. With respect to genetics, *"because environmental factors influence the expression of genes, and genes influence the environment individuals live in, there is probably no 'true' heritability of depression; that is, genetic liability for depression most probably varies under different environmental factors … Studies have shown, for example, that social support is for a substantial part genetically determined through the effects of temperament and personality* [53]*."* As a consequence, depression should be seen as a culturally and developmentally influenced disorder *[*54]. The same is true for functional pain syndromes, with genetics pointing to both central and end-organ influences. In other words, there is a genetic basis for spinal degeneration, but there is also a genetic basis for pain sensitivity, with heritability for pain perception across several experimental modalities and pain syndromes ranging from 22% to 60% [55-56]. Common genetic pleiotropic effects exist for functional pain syndromes, cognitive disorders and affective disorders [57].

Throughout, we see patterns of meaning both in normalcy and disorder, with the boundaries between the two both being diffuse. We hypothesize that, at the SP level, a highly generalized meta-pattern is the causal basis of all affective spectrum disorders. This is not any specific pattern, but the way that patterns are or are not realized. Specifically, if meaningful patterns are frequently initiated but then aborted prior to completion, this can create inner tensions that in time manifest themselves as anxiety, depression, chronic pain, and so on. We see strong arguments for this in the influence of emotions on pain.

Influence of emotions on chronic pain

Psychological factors and organ-related pathologies may exist in a complex relationship with each other. As Mayer and Bushnell note, *"it is conceivable that in a subset of patients with other risk factors to develop a chronic pain syndrome, organ-related pathologies (disk degeneration, latent bladder infections, altered intestinal microflora, mechanical temporomandibular joint changes) or a history of an acute organ-related injury may be required to produce the full clinical syndrome."* [50] In addition, organ-related pathologies may themselves be the result of interplay with psychological factors, possibly due to self-perpetuating patterns.

In early decades of psychosomatic medicine, much interest was focused on emotional conflicts and defenses, and on the way they influence chronic pain. This interest then started to wane in the 1960s, so that, by the beginning of the 1990s, most prevailing models were based upon cognitive-behavioral learning principles (conditioning and other learning processes). However, since the 1990s, basic and applied research has once again focused increasingly on emotions and their regulatory role in pain control [58]. For example, a retrospective study of 244 females who did not initially have temporomandibular joint disorder found that somatization, anxiety, depression and perceived stress were significant risk factors (from 2.1 to 6.0) for subsequent onset [59]. Increasingly, neuroimaging studies show that the activity in pain pathways is altered by attentional states [60], positive and negative emotions, empathy, and other factors [61]. Furthermore, physical and emotional pain share many of the same central nervous system pathways [62], which can, for example, be demonstrated by visualizing the emotional pain of social exclusion [63].

In general, changes of 'pain' induced by emotion affect pain unpleasantness ratings more than pain intensity ratings. Positive emotions decrease pain, while negative emotions have the opposite effect [61]. Autonomic responses evoked by pain are also more strongly associated with pain affect [64]. Conversely, negative emotions are triggered by the immediate unpleasantness of pain, and by the cognitive interpretation of the meaning of pain and its future consequences [64]. It is not always easy to see which comes first.

Pain demands attention [65], but attention mechanisms also contribute to the effects of emotion on pain [65]. Attention modulation is probably the most-studied psychological variable that modifies the pain experience. According to Kenntner-Mabiala et al., manipulation of attention specifically influences pain intensity ratings

(and not affect), presumably mediated by the primary somatosensory cortex. Pain reduction due to treatment can sometimes be explained entirely by the redirection of attention away from the pain [66], but the results of other studies are less easily interpreted [67]. However, the idea that attention modulates pain in some way correlates well with neuroimaging studies [68] [66]. In the experience of one of the authors (Mommaerts), this modulation is related to the *type* of attention involved (fearful, catastrophizing, relaxed, accepting, and so on). Research into undifferentiated attention may thus not lead to valid results.

The strong influence of emotions and beliefs upon chronic pain is proof that mind can influence chronic pain. In the case of chronic pain however, underlying emotions and the causes of these emotions (which may be further emotions or beliefs with still other causes, of which the patient may or may not be consciously aware) should be taken into consideration. Viewing pain as the 'culprit' may not conform to the reality of the patient, and may be a reason why patients look elsewhere for more 'holistic' help.

Present-day treatment of chronic pain

Regardless of the type of therapy, it is a consistent finding that chronic pain patients vary substantially in their responses [69]. Furthermore, many patients find their pain is recalcitrant to all available treatments [32].

Radiographic findings for conditions such as chronic back pain are poorly related to pain severity and disability [70-73]. Generally, there is little relation between pain intensity and disability among patients with chronic pain [74-76]. Therefore, a therapy that leads to significant pain reduction may not produce any change in perceived function [77].

As chronic pain is more related to meaning than acute pain, CFP syndromes are generally resistant to treatments that are effective for acute pain [78]. For example, while initially beneficial, long-term opiate therapy for chronic pain gives discouraging results, due to a myriad of compensatory actions and reactions that inevitably impair opioid receptor activation and facilitate pain transmission [79-82]. Over the last few decades, there has been a significant increase in the use of opioids for chronic non-cancer pain [83], without significant evidence from long-term studies as to the safety of this practice. A systematic review of long-term opioid use only revealed studies with a maximum length of 8 weeks [84]. An epidemiological

study in Denmark (2006; N=10.066) evaluated real-life long-term effects of opioids in non-cancer chronic pain sufferers, and found that opioid treatment *"does not seem to fulfill any of the key outcome opioid treatment goals: pain relief, improved quality of life and improved functional capacity."* [83] According to the authors, opioids can have *"relatively short-run (months) benefits in relief of chronic pain, which in the long run (years) may turn into opposite and deleterious effects as previously described by* [85] *as 'the opioid downhill spiral'"*. There is a growing body of evidence, based on animal and human studies, that chronic opioid exposure *increases* sensitivity to pain. Methadone-maintained addicts [86-87], as well as other opioid-addicted populations [88-89], are hyperalgesic when compared to normal control subjects. Similar hyperalgesia is found in chronic pain patients treated with morphine [90-91]. Natural opioid-based inhibitory systems seem to be designed for short-term pain control. This may also partly explain how and why psychological stress reduces pain sensitivity during acute emergencies, while leading to stress-induced hyperalgesia over the long term [92] and facilitating the development of chronic pain. Factors responsible for maintaining or even worsening pain can be seen in synaptic mechanisms as well as in neuronal patterns. Hypersensitivity mechanisms at this level have been investigated in many domains aside from pain, including vision and audition.

Specific techniques account for about 15% of positive outcomes in psychosocial treatments for depression. In cognitive-behavioral therapy (CBT) studies, most of the therapeutic gain is observed in the first few sessions, before specific techniques are used [93]. Systematic reviews show that CBT for CFP is effective over the short term, including improvements in pain intensity and functioning [94-96]. However, long-term maintenance of improvements is not well documented. Also, it is not clear which components of CBT actually work. For example, a randomized controlled trial (RCT) where CBT was used to treat patients with chronic temporomandibular disorder showed improvement in pain intensity and interference with activities. However, change in *perceived* pain control mediated the largest proportion of the total treatment effect [97]. In a cohort study of cancer pain relief (N=94), a cognitive-behavioral skills package including relaxation and imagery resulted in less pain, but did not show an additive effect beyond relaxation and imagery alone [98]. In general, there is little current evidence that psychosocial 'empirically supported treatments' produce changes in chronic pain or depression that are consistent with theory [54]. As with chronic pain, there is a lack of well-designed RCTs addressing the long-term outcome of such treatments with depression. Westen and Morrison only found two

studies with two years or more of follow-up data, and, only 8% of the patients originally screened in these studies avoided a relapse during that time [99].

Regardless of the type of psychotherapeutic treatment, long-term treatment is becoming the rule rather than the exception in the treatment of depression, as is the case with chronic pain. After decades of long and costly psychodynamic psychotherapy, it seemed appropriate to search for brief and less costly therapies such as CBT, encouraged by the view of depression as a disease that should have a straightforward cure. However, the last three decades have shown that this approach does not produce lasting effects in most patients. The present direction is to develop long-term versions of short-term treatments.

Pain-related placebo

In all of this, however, one element that 'works' consistently is the placebo.

Research shows that the 'working' element in a placebo is the suggestion that envelops it [3,100]. For example, the addition of verbal analgesic suggestions can increase placebo analgesia to the level of an active agent [101]. The greatest placebo effect occurs in highly suggestible patients [102], especially after they have had positive experiences with analgesic treatment [103]. Functional neuroimaging shows that placebo analgesia affects the sensory, affective and cognitive dimensions of the pain experience [104]. In congruence with SPT, different suggestions accompanying analgesic placebos lead to different results. Experiments with positron emission tomography (PET) show somatosensory cortex activity is inhibited by suggestions specifically developed for *sensory* analgesia [105], while suggestions for *affective* pain reduction cause alterations in the part of the brain that processes emotional information [106].

Clearly, placebo analgesia can activate diverse modulatory systems in the brain, including those that are stimulated by opiates given for pain relief. In addition, it activates antinociceptive pathways that start in the limbic forebrain and are relayed through the periaqueductal gray matter to primary afferent nociceptive sites in the spinal cord dorsal horn [107]. Goffaux et al. showed in their neurophysiological studies that expectation-based analgesia, as engendered by placebos, depends on both descending spinal inhibition and cortical activity, suggesting that multiple pathways must underlie expectation effects [107]. Analgesic placebos clearly provoke a cascade of changes that result from activity at multiple levels [104,108].

Endorphins, via opioid neurotransmission in the anterior cingulated cortex (ACC), orbitofrontal and insular cortices, nucleus accumbens, amygdalae and periaqueductal gray matter, are positively associated with anticipated and subjectively perceived effectiveness, and with reduction in continuous pain ratings [109], while being negatively associated with nocebos [109]. Regional dopamine activation in ventral basal ganglia is also positively associated with the analgesic placebo effect and negatively associated with nocebos [109]. Substance-P, identified as the primary nociceptive transmitter in afferent sensory fibers and shown to be influenced by placebos, is related to the integration of pain, stress and anxiety. Many other biochemicals may be influenced by placebos, including cholecystokinin, serotonin, adenosines, bradykinin, prostaglandins and cytokines. There is no magic involved in this, since biochemicals do not change miraculously due to an 'immaterial psyche'. Again, SPT is a sufficient explanation for this, and is compatible with all analgesic placebo research data.

This is not just important for our understanding of the way placebos influence pain. For instance, dopaminergic and opioid systems modulate many other processes, including affective states, neuroendocrine, immunological and cardiovascular functions, and the effects of substance abuse. In exploiting these systems, psychological interventions that specifically target SP may affect the capacity to influence the risk factors of various illnesses, as well as their progression.

Subconceptual processing and treatment of chronic pain

Up until now, the management of CFP has mainly come down to attempts to control the pain, even to 'kill' the pain, as in 'painkillers'. This is logical if the pain is a meaningless consequence of an underlying cause. However, if CFP is not meaningless, as is asserted by SPT, then 'painkilling' is, at best, an incomplete approach. Furthermore, the underlying cause of CFP may be related to meaning and is, in most cases, not properly addressed at present in our view. Such a stance would be unacceptable, for instance, with cancer pain. From a SPT perspective, this may even have the ironic effect of creating *more* suffering across all syndromes in the long term, instead of less. Such effects have been documented with conceptual empathy in chronic pain caregivers [4], in the long-term use of antidepressants and of painkillers such as morphine, and, even more clearly and relevantly, in chronic anger suppression leading to increased pain intensity in chronic pain patients [110-115].

This is difficult to investigate scientifically. As RCTs are habitually conducted over very short time periods (mostly weeks), they are of no value for chronic syndromes, let alone for real patients whose syndromes last most of their life. This situation will not easily be remedied. As one delves deeper, problems grow exponentially, since confounding factors are exponentially harder to control. RCTs and meta-analyses by themselves are not enough to solve the problems of real patients, and if we retain these tools as a 'Gold standard ', the problem becomes intractable. As in any hard science such as chemistry, biology or physics, we need not only facts but also good theoretical frameworks that conform to the facts and vice versa. 'Only facts' conceals an *implicit* theory of Cartesian dualism on which medicine is still mainly based, despite the theory being discarded long ago.

SPT is aligned with a growing volume of data from many domains of mental processing, with human vision being particularly well investigated [1,116-117]. With regards to chronic pain, little to no progress has been made so far to our knowledge. However, placebos can be seen as one way of profoundly influencing subconceptual patterns, albeit with only one message: "I will get better." This single message is probably the reason why it is so powerful and focused. It is far from evident, however, that this is the best approach, even if it relieves symptoms temporarily. Symptoms may come back or, given their common underlying nature, one syndrome can replace another.

What 'works' is subconceptual communication or suggestion, of which the placebo effect is one example. Suggestion has also been shown to increase pain, with a study by Colloca et al. demonstrating that verbal suggestions could turn low-intensity pain stimuli into high-intensity pain [118]. Other studies show pain thresholds increase and decrease following positive and negative suggestions [119]. This illustrates the need to explore subconceptual communication in more depth. Hypnosis is an interesting domain for this, as hypnotic suggestions having no advantage over suggestions alone [120-122].

Placebo in most cases comes down to controlling the subconscious or getting rid of it (which is also a way of controlling it). One can also see this in mainstream psychotherapies, whether psychoanalytical, mainly 'controlling it', or cognitive-behavioral black-box-like, mainly 'getting rid of it'. The recurring idea is: if one can control the subconscious, one can control the pain. Contrary to this, studies show that aggressively controlling chronic pain is specifically not effective [123]. We

should not so much try to aggressively control the pain, as to 'communicate' non-aggressively to subconceptual patterns as exemplified by a proper kind of empathy [4].

Subconceptual communication is an activity that patients can largely do on their own, given appropriate tools and support. This is a very ethical undertaking that needs openness, respect and trust. The mounting burden of chronic pain on health care systems puts increased focus on the importance of effective self-management. It is a valuable goal for chronic pain [124], which can be addressed optimally within the framework of SPT.

While anxiety and depression are firmly correlated (both epidemiologically and clinically) with the presence and degree of chronic pain, it does not seem necessary to treat either of these conditions for pain symptoms to improve [125], nor does treatment necessarily cause improvement. Additionally, depressed patients with pain are often chronically depressed and more difficult to treat than those without pain [126], which may be explained by mutual causality. Thus, a treatment that only addresses the symptoms of anxiety or depression may have little influence on chronic pain, but if the treatment goes deeper and addresses the shared cause, it may have a positive effect on both. Research into this area could be of great interest.

We also believe it is important to address the vexed question of whether CFP (along with other conditions such as chronic fatigue syndrome) is 'all in the head' – with all the negative connotations that implies – or is 'real' and related to the body. With SPT, both answers are the same and the question is moot. However, SP acts as a nonspecific factor at the subconscious level, giving the impression that it is not related to the conscious mind, and therefore is part of a separate body. Because of this, many patients and their caregivers are stuck in a fog. Clearing this fog in a manner that is compatible with science may lead to therapeutic management for many who do not receive it at present, including a number who are misled into sham treatments.

Conclusion

Increasingly, CFP syndromes are being conceptually unified into one underlying condition and investigated as such, but insights are hampered by siloed thinking promoted by subspecialized medicine. Factors related to the brain/mind play an enormous role in this, when contrasted with the peripheral factors at the fore of

organ-specific 'pain syndromes'. Meanwhile, we are seeing a burgeoning chronic pain problem. Present-day therapies such as spinal surgery and long-term administration of morphine are increasingly controversial, since they are very costly for individuals as well as for society, have significant side effects and, in many cases, clearly deliver unsatisfactory results with respect to pain and disability. In addition, many in the field see the search for better therapies as clearly unpromising. New insight into the true power of placebos adds significantly to this controversy. However, the failure of available therapies shows the need for a paradigm shift, which may come from putting SPT at the center of CFP management. Increasingly, cognitive neuroscience data is showing the worth of SPT in many human mental processing domains. The use of this knowledge with CFP is, however, ethically challenging, in that openness, respect and trust are key issues, and are incompatible with a simple choice to use placebos, even if placebos diminish symptoms temporarily.

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References

1 Churchland PS. *Brain-wise : studies in neurophilosophy*. Cambridge, Mass.: MIT Press, 2002.

2 Rumelhart DE, McClelland JL, University of California San Diego. PDP Research Group. *Parallel distributed processing : explorations in the microstructure of cognition*. Cambridge, Mass.: MIT Press, 1986.

3 Mommaerts JL, Devroey D. The placebo effect: how the subconscious fits in. *Perspect Biol Med* 2012;**55**:43-58.

4 Mommaerts JL, Goubert L, Devroey D. Empathy beyond the conceptual level: core nonspecific factors of psychotherapy. *Perspect Biol Med* 2012;**55**:175-82.

5 Melzack R, Wall PD. *Handbook of pain management*. Edinburgh: Churchill Livingstone, 2003.

6 Chodosh J, Ferrell BA, Shekelle PG, Wenger NS. Quality indicators for pain management in vulnerable elders. *Ann Intern Med* 2001;**135**:731-5.

7 Goudas L, Carr DB, Bloch R, Balk E, Ioannidis JP, Terrin N, Gialeli-Goudas M, Chew P, Lau J. Management of cancer pain. *Evid Rep Technol Assess (Summ)* 2001:1-5.

8 Cousins MJ, Brennan F, Carr DB. Pain relief: a universal human right. *Pain* 2004;**112**:1-4.

9 McCaffery M. *Nursing management of the patient with pain*. 3d edn. Philadelphia: Lippincott, 2000.

10 Duncan G. Mind-body dualism and the biopsychosocial model of pain: what did Descartes really say? *J Med Philos* 2000;**25**:485-513.

11 Merskey H, Bogduk N. *Classification of chronic pain : descriptions of chronic pain syndromes and definitions of pain terms*. 2nd edn. Seattle: IASP Press, 1994.

12 Von Korff M, Dunn KM. Chronic pain reconsidered. *Pain* 2008;**138**:267-76.

13 Boersma K, Linton SJ. Expectancy, fear and pain in the prediction of chronic pain and disability: a prospective analysis. *Eur J Pain* 2006;**10**:551-57.

14 Neugebauer V. The amygdala: different pains, different mechanisms. *Pain* 2007;**127**:1-2. Epub 2006 Nov 22.

15 Fordyce WE. *Behavioral methods for chronic pain and illness*. Saint Louis: Mosby, 1976.

16 Melzack R, Wall PD. *The challenge of pain*. New York: Basic Books, 1983.

17 Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science. *J Pain* 2004;**5**:195-211.

18 Turk DC, Meichenbaum D, Genest M. *Pain and behavioral medicine : a cognitive-behavioral perspective*. New York: Guilford Press, 1983.

19 Melzack R, Katz J. The McGill pain questionnaire: appraisal and current status. In: Turk DC, Melzack R, eds. Handbook of pain assessment, 2nd edn. New York: Guilford Press, 2001:35–52.

20 Flor H, Turk DC. Chronic back pain and rheumatoid arthritis: predicting pain and disability from cognitive variables. *J Behav Med* 1988;**11**:251-65.

21 Turk D, Melzack R. The Measurement of Pain and the Assessment of People Experiencing Pain. In: Turk DC, Melzack R, eds. Handbook of pain assessment, 2nd edn. New York: Guilford Press, 2001:1–11.

22 Melzack R, Casey KL. Sensory, motivational and central control determinants of pain: a new conceptual model. In: Kenshalo DR, ed. The skin senses; proceedings. Springfield, Ill.: Thomas, 1968:423-43.

23 Jenson MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk DC, Melzack R, eds. Handbook of pain assessment. 2nd edn. New York: Guilford Press, 2001:135–151.

24 Lanzetta JT, Cartwright-Smith J, Kleck RE. Effects of nonverbal dissimulation on emotional experience and autonomic arousal. *J Pers Soc Psychol* 1976;**33**:354-70.

25 Ingvar M, Hsieh J. The image of pain. In: Wall P, Melzack R eds. The textbook of pain. Edinburgh: Churchill Livingstone, 1999: 215–34.

26 Brooks JC, Tracey I. The insula: a multidimensional integration site for pain. *Pain* 2007;**128**:1-2.

27 Melzack R. Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. *Pain Pract* 2005;**5**:85-94.

28 Moseley GL. A pain neuromatrix approach to patients with chronic pain. *Man Ther* 2003;**8**:130-40.

29 Niedenthal P, Kitayama S eds. *The heart's eye*. San Diego: Academic Press, 1994

30 Robinson JP, Apkarian AV. Low back pain. In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle: IASP Press, 2009: 23-54.

31 Bremner JD. Combat-related psychiatric stresses. In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle: IASP Press, 2009:169-184.

32 Turk DC. Understanding pain sufferers: the role of cognitive processes. *Spine J* 2004;**4**:1-7.

33 Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: a population study. *Pain* 2006;**123**:19-27.

34 Maixner, W. Temporomandibular disorders. In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle:IASP Press, 2009:55-70.

35 Derbyshire SW, Jones AK, Creed F, Starz T, Meltzer CC, Townsend DW, Peterson AM, Firestone L. Cerebral responses to noxious thermal stimulation in chronic low back pain patients and normal controls. *Neuroimage* 2002;**16**:158-68.

36 Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. *N Engl J Med* 1994;**331**:69-73.

37 DeCarvalho LT, Whealin JM. What pain specialists need to know about posttraumatic stress disorder in Operation Iraqi Freedom returnees. *J Musculoskel Pain* 2006:**14**;37-45

38 Sela RA, Bruera E, Conner-spady B, Cumming C, Walker C. Sensory and affective dimensions of advanced cancer pain. *Psychooncology* 2002;**11**:23-34.

39 Mayer EA, Bushnell MC. Preface. In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle: IASP Press, 2009:xv.

40 Demyttenaere K, Bruffaerts R, Lee S, Posada-Villa J, Kovess V, Angermeyer MC, Levinson D, de Girolamo G, Nakane H, Mneimneh Z, Lara C, de Graaf R, Scott KM, Gureje O, Stein DJ, Haro JM, Bromet EJ, Kessler RC, Alonso J, Von Korff M. Mental disorders among persons with chronic back or neck pain: results from the World Mental Health Surveys. *Pain* 2007;**129**:332-42.

41 Diatchenko L, Nackley AG, Slade GD, Fillingim RB, Maixner W. Idiopathic pain disorders--pathways of vulnerability. *Pain* 2006;**123**:226-30.

42 Macdonald G, Leary MR. Why does social exclusion hurt? The relationship between social and physical pain. *Psychol Bull* 2005;**131**:202-23.

43 Kato K, Sullivan PF, Evengard B, Pedersen NL. Chronic widespread pain and its comorbidities: a population-based study. *Arch Intern Med* 2006;**166**:1649-54.

44 Ahmed S, Schatzberg AF, Friedman ES, Rothschild AJ, Trivedi MH, Dunner DL, Gelenberg A, Ninan P, Shelton R, Zajecka JM. Prevalence and clinical correlates of pain in patients with recurrent major depressive disorder. *Er Neuropsychopharmacol 2007*;**17**:S320-21

45 Perahia DG, Quail D, Desaiah D, Montejo AL, Schatzberg AF. Switching to duloxetine in selective serotonin reuptake inhibitor non- and partial-responders: effects on painful physical symptoms of depression. *J Psychiatr Res* 2009;**43**:512-18.

46 Bremner JD. Does stress damage the brain? Understanding trauma-related disorders from a mind-body perspective. New York: Norton, 2002

47 Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. *Prog Brain Res* 2008;**167**:171-86.

48 Francati V, Vermetten E, Bremner JD. Functional neuroimaging studies in posttraumatic stress disorder: review of current methods and findings. *Depress Anxiety* 2007;**24**:202-18.

49 Clauw DJ, Williams DA. Fibromyalgia. In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle:IASP Press, 2009:3-22.

50 Polich G, Kong J, Napadow V, Gollub R. Functional pain disorders: time for a paradigm shift? In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle: IASP Press, 2009: 531-560.

51 Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle:IASP Press, 2009.

52 Engel GL. Psychogenic pain and pain-prone patient. *Am J Med* 1959;**26**:899-918.

53 Kendler KS, Myers J, Prescott CA. Sex differences in the relationship between social support and risk for major depression: a longitudinal study of opposite-sex twin pairs. *Am J Psychiatry* 2005;**162**:250-56.

54 Luyten P, Blatt SJ, Van Houdenhove B, Corveleyn J. Depression research and treatment: are we skating to where the puck is going to be? *Clin Psychol Rev* 2006;**26**:985-99.

55 Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. *Pain* 2008;**136**:21-29.

56 Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB. Heritability of responses to painful stimuli in women: a classical twin study. *Brain* 2007;**130**:3041-49.

57 Oroszi G, Goldman D. Alcoholism: genes and mechanisms. *Pharmacogenomics* 2004;**5**:1037-48.

58 Keefe FJ, Lumley M, Anderson T, Lynch T, Studts JL, Carson KL. Pain and emotion: new research directions. *J Clin Psychol* 2001;**57**:587-607.

59 Slade GD, Diatchenko L, Bhalang K, Sigurdsson A, Fillingim RB, Belfer I, Max MB, Goldman D, Maixner W. Influence of psychological factors on risk of temporomandibular disorders. *J Dent Res* 2007;**86**:1120-25.

60 Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. *Brain* 2002;**125**:310-9.

61 Loggia ML, Schweinhardt P, Villemure C, Bushnell MC. Effects of psychological state on pain perception in the dental environment. *J Can Dent Assoc* 2008;**74**:651-56.

62 Van Houdenhove B, Luyten P. Beyond dualism: the role of life stress in chronic pain. *Pain* 2005;**113**:238-9; discussion 40-2.

63 Eisenberger NI, Jarcho JM, Lieberman MD, Naliboff BD. An experimental study of shared sensitivity to physical pain and social rejection. *Pain* 2006;**126**:132-8.

64 Rainville P, Bao QV, Chretien P. Pain-related emotions modulate experimental pain perception and autonomic responses. *Pain* 2005;**118**:306-18.

65 Villemure C, Bushnell MC. Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain* 2002;**95**:195-9.

66 Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B. Pain perception: is there a role for primary somatosensory cortex? *Proc Natl Acad Sci U S A* 1999;**96**:7705-9.

67 Levine JD, Gordon NC, Smith R, Fields HL. Post-operative pain: effect of extent of injury and attention. *Brain Res* 1982;**234**:500-4.

68 Meyer E, Ferguson SS, Zatorre RJ, Alivisatos B, Marrett S, Evans AC, Hakim AM. Attention modulates somatosensory cerebral blood flow response to vibrotactile stimulation as measured by positron emission tomography. *Ann Neurol* 1991;**29**:440-3.

69 Morley S, Keefe FJ. Getting a handle on process and change in CBT for chronic pain. *Pain* 2007;**127**:197-8.

70 Beattie PF, Meyers SP, Stratford P, Millard RW, Hollenberg GM. Associations between patient report of symptoms and anatomic impairment visible on lumbar magnetic resonance imaging. *Spine (Phila Pa 1976)* 2000;**25**:819-28.

71 Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. *J Bone Joint Surg Am* 1990;**72**:403-8.

72 Greenberg JO, Schnell RG. Magnetic resonance imaging of the lumbar spine in asymptomatic adults. Cooperative study--American Society of Neuroimaging. *J Neuroimaging* 1991;**1**:2-7.

73 Weishaupt D, Zanetti M, Hodler J, Boos N. MR imaging of the lumbar spine: prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. *Radiology* 1998;**209**:661-6.

74 Geisser ME, Roth RS Knowledge of and agreement with pain diagnosis: Relation to pain beliefs, pain severity, disability, and psychological distress. *J Occup Rehabil* 1998;**8**:73-88.

75 Millard RW, Wells N, Thebarge RW. A comparison of models describing reports of disability associated with chronic pain. *Clin J Pain* 1991;**7**:283-91.

76 Vlaeyen JWS, Kole-Snidjers AMJ, Rotteveel AM, Rvesink R, Heuts PHTG. The role of fear of movement/(re)injury in pain disability. *J Occup Rehabil* 1995:**5**:235-52.

77 Geisser ME, Wiggert EA, Haig AJ, Colwell MO. A randomized, controlled trial of manual therapy and specific adjuvant exercise for chronic low back pain. *Clin J Pain* 2005;**21**:463-70.

78 Light K, Vierck CJ. HPA axis and sympathetic influences on pain an fatigue in fibromyalgia, chronic fatigue, and overlapping functional pain syndromes. In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle: IASP Press, 2009:301-318.

79 Haller VL, Bernstein MA, Welch SP. Chronic morphine treatment decreases the Cav1.3 subunit of the L-type calcium channel. *Eur J Pharmacol* 2008;**578**:101-7.

80 Mayer DJ, Mao J, Holt J, Price DD. Cellular mechanisms of neuropathic pain, morphine tolerance, and their interactions. *Proc Natl Acad Sci U S A* 1999;**96**:7731-6.

81 McCleane GJ. The cholecystokinin antagonist proglumide enhances the analgesic effect of dihydrocodeine. *Clin J Pain* 2003;**19**:200-1.

82 Yue X, Tumati S, Navratilova E, Strop D, St John PA, Vanderah TW, Roeske WR, Yamamura HI, Varga EV. Sustained morphine treatment augments basal CGRP release from cultured primary sensory neurons in a Raf-1 dependent manner. *Eur J Pharmacol* 2008;**584**:272-7.

83 Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain* 2006;**125**:172-9.

84 Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain* 2004;**112**:372-80.

85 Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of nonmalignant origin. *J Pain Symptom Manage* 1993;**8**:279-88.

86 Compton MA. Cold-pressor pain tolerance in opiate and cocaine abusers: correlates of drug type and use status. *J Pain Symptom Manage* 1994;**9**:462-73.

87 Ho A, Dole VP. Pain perception in drug-free and in methadone-maintained human ex-addicts. *Proc Soc Exp Biol Med* 1979;**162**:392-5.

88 Ling W, Cunningham-Rathner J, Fradis J, Torrington M, Keating M, White J. Opioid-induced hyperalgesia: Effects of buprenorphine treatment. Presented at the Meeting of the College on Problems of Drug Dependence, Miami, FL. 2003.

89 Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: New evidence from a study of chronic opioid addicts and healthy subjects. *Drug Alcohol Depend* 2006;**82**:218-23.

90 Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. *J Pain* 2009;**10**:316-22.

91 Mitchell TB, White JM, Somogyi AA, Bochner F. Switching between methadone and morphine for maintenance treatment of opioid dependence: impact on pain sensitivity and mood status. *Am J Addict* 2006;**15**:311-5.

92 King CD, Devine DP, Vierck CJ, Mauderli A, Yezierski RP. Opioid modulation of reflex versus operant responses following stress in the rat. *Neuroscience* 2007;**147**:174-82.

93 Parker G, Roy K, Eyers K. Cognitive behavior therapy for depression? Choose horses for courses. *Am J Psychiatry* 2003;**160**:825-34.

94 Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: systematic review. *BMJ* 2001;**322**:1511-6.

95 Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. *Health Psychol* 2007;**26**:1-9.

96 Ostelo RW, van Tulder MW, Vlaeyen JW, Linton SJ, Morley SJ, Assendelft WJ. Behavioural treatment for chronic low-back pain. *Cochrane Database Syst Rev* 2005:CD002014.

97 Turner JA, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. *Pain* 2007;**127**:276-86.

98 Syrjala KL, Donaldson GW, Davis MW, Kippes ME, Carr JE. Relaxation and imagery and cognitive-behavioral training reduce pain during cancer treatment: a controlled clinical trial. *Pain* 1995;**63**:189-98.

99 Westen D, Morrison K. A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: an empirical examination of the status of empirically supported therapies. *J Consult Clin Psychol* 2001;**69**:875-99.

100 Stam HJ, Spanos NP. Hypnotic analgesia, placebo analgesia, and ischemic pain: the effects of contextual variables. *J Abnorm Psychol* 1987;**96**:313-20.

101 Vase L, Robinson ME, Verne GN, Price DD. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation. *Pain* 2003;**105**:17-25.

102 De Pascalis V, Chiaradia C, Carotenuto E. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. *Pain* 2002;**96**:393-402.

103 Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain* 2006;**124**:126-33.

104 Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 2004;**303**:1162-7.

105 Hofbauer RK, Rainville P, Duncan GH, Bushnell MC. Cortical representation of the sensory dimension of pain. *J Neurophysiol* 2001;**86**:402-11.

106 Patterson DR, Jensen MP. Hypnosis and clinical pain. *Psychol Bull* 2003;**129**:495-521.

107 Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia--when the spine echoes what the brain expects. *Pain* 2007;**130**:137-43.

108 Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain* 2007;**127**:63-72.

109 Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry* 2008;**65**:220-31.

110 Burns JW, Quartana PJ, Bruehl S. Anger inhibition and pain: conceptualizations, evidence and new directions. *J Behav Med* 2008;**31**:259-79.

111 Burns JW, Quartana P, Gilliam W, Gray E, Matsuura J, Nappi C, Wolfe B, Lofland K. Effects of anger suppression on pain severity and pain behaviors among chronic pain patients: evaluation of an ironic process model. *Health Psychol* 2008;**27**:645-52.

112 Greenwood KA, Thurston R, Rumble M, Waters SJ, Keefe FJ. Anger and persistent pain: current status and future directions. *Pain* 2003;**103**:1-5.

113 Quartana PJ, Burns JW. Painful consequences of anger suppression. *Emotion* 2007;**7**:400-14.

114 Quartana PJ, Yoon KL, Burns JW. Anger suppression, ironic processes and pain. *J Behav Med* 2007;**30**:455-69.

115 Venable VL, Carlson CR, Wilson J. The role of anger and depression in recurrent headache. *Headache* 2001;**41**:21-30.

116 Churchland PS, Sejnowski TJ. The computational brain. Cambridge, Mass: MIT Press, 1992.

117 Bechtel W, Abrahamsen A. Connectionism and the mind. Oxford: Blackwell, 1994.

118 Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. *Pain* 2008;**136**:211-8.

119 Staats P, Hekmat H, Staats A. Suggestion/placebo effects on pain: negative as well as positive. *J Pain Symptom Manage* 1998;**15**:235-43.

120 Milling LS, Kirsch I, Allen GJ, Reutenauer EL. The effects of hypnotic and nonhypnotic imaginative suggestion on pain. *Ann Behav Med* 2005;**29**:116-27.

121 Spanos NP, McNeil C, Gwynn MI, Stam HJ. Effects of suggestion and distraction on reported pain in subjects high and low on hypnotic susceptibility. *J Abnorm Psychol* 1984;**93**:277-84.

122 Rainville P, Carrier B, Hofbauer RK, Bushnell MC, Duncan GH. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. *Pain* 1999;**82**:159-71.

123 Whitman SM. Pain and suffering as viewed by the Hindu religion. *J Pain* 2007;**8**:607-13.

124 Borkan JM, Cherkin DC. An agenda for primary care research on low back pain. *Spine (Phila Pa 1976)* 1996;**21**:2880-4.

125 Naliboff BD, Rhudy, JL. Anxiety in functional pain disorders. In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle: IASP Press, 2009:185-214

126 Schatzberg, AF. Chronic pain and depression. In: Mayer EA, Bushnell MC eds. Functional pain syndromes: presentation and pathophysiology. Seattle: IASP Press, 2009:215:226.

Prerecorded Autosuggestion for Long-lasting Pain Intervention (PALPI-study).

This describes a scientific initiative to investigate the impact of autosuggestion on chronic pain. This is a clear opportunity for the future, provided that needed resources are available. We would very much like to continue and use this PALPI study as a pilot for many subsequent studies.

4.17 CONGRESS ENTRY: Prerecorded Autosuggestion for Long-lasting Pain Intervention (PALPI-study).

Wetenschapsdag Domus Medica, Vrije Universiteit Brussel, Brussel 2010

Introduction

The objective of this study (as part of a PhD) is to investigate the hypothesis that prerecorded autosuggestion (PA) can be a theoretically valuable (efficacy) and practical (efficiency) tool in the care of many patients with chronic pain.

A number of GPs will be contacted. A working definition of 'chronic pain patient' is put forward. Only patients with chronic pain for which present research suspects a substantial degree of psychosomatic causality are withheld. A randomization of these into three groups is performed by the appropriate department of the VUB. The three groups are: a control group (receiving 'care as usual'), a group receiving additionally to care as usual, 5 autosuggestion CDs (containing +/- 25 different sessions of autosuggestion) and a group receiving additionally to care as usual, email assistance (through a specific internet module), including downloadable CDs as appropriate and access to 'AurelisOnLine' (an internet application with > 1100 different sessions of autosuggestion). Three of the CDs contain pre-recorded sessions of relaxation + autosuggestion aimed at diminishing pain. Other CDs are about relaxation, general wellness, etc. Each arm of investigation contains 30 subjects. Assessments are made at 3 points in time: at the start, at 1 month from the start and at 3 months from the start. The following will be measured: quality of life (through a Dutch version of the WHYMPI-scale), levels of pain intensity and quality (through a Dutch version of MPQ) and use of painkillers. In addition to this, the acceptance/satisfaction of physicians and patients of this kind of treatment will also be the subject of this investigation.

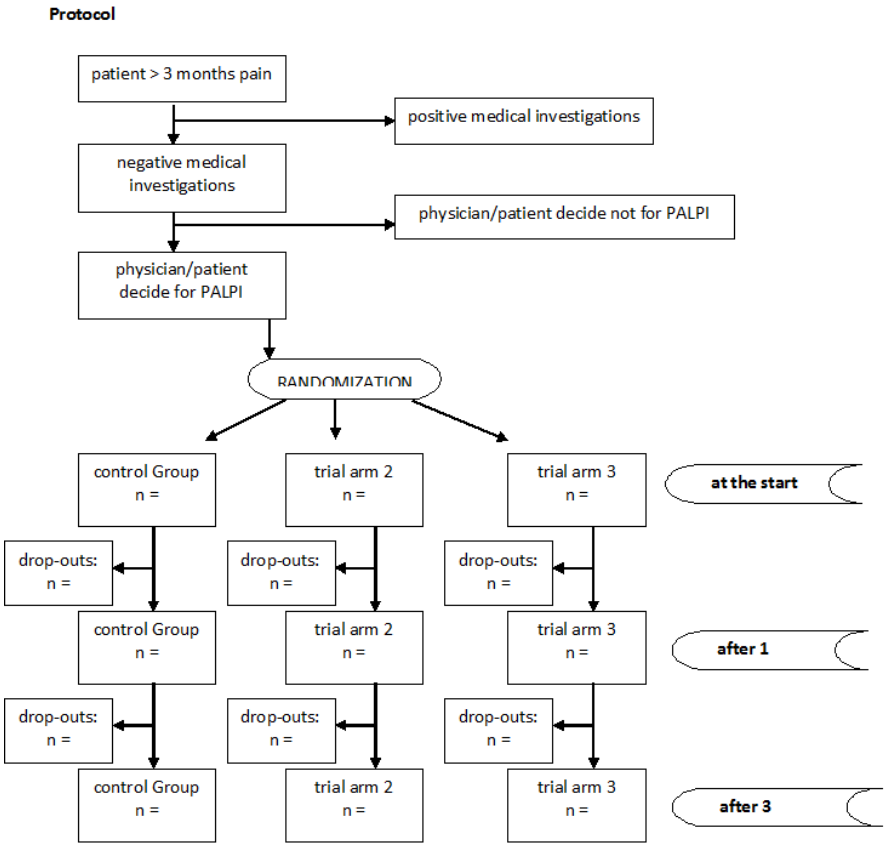
Null hypotheses

We perform hypothesis testing. Null hypotheses are:

- The use of PALPI-trial arm 2 has no influence upon
    - sensory aspect of pain (~MPQ-PRI-S)

- affective aspect of pain (~MPQ-PRI-A)
- evaluative aspect of pain (~MPQ-PRI-E)
- totality of former 3 + 'miscellaneous' category of the MPQ - (~MPQ-PRI-T)
- pain intensity (~MPQ-PPI and MPI section 1)
- pain interference (~MPI section 1)
- support (~MPI section 1)
- life-control (~MPI section 1)
- daily activities (~MPI section 3)

- The use of PALPI-trial arm 3 has no influence upon these same items.



Placebo as Communication to Neur(on)al Networks in Chronic Functional Pain

This article places placebos within the context of subconceptual processing, and examines the practical implications of this for etiology and management of chronic functional pain. In this area, ancient Eastern insights and modern Western science come together to show us paths towards inner strength and healing in pain and many other domains. Communication occurs through overlapping patterns both inside and outside the mind. These patterns can be seen as material or immaterial depending on the viewpoint taken.

4.18 CONGRESS ENTRY: Placebo as Communication to Neur(on)al Networks in Chronic Functional Pain

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Abbreviations: Subconceptual Processing Level (SPL); Subconceptual Processing Theory (SPT); Parallel Distributed Processing (PDP); Complementary & Alternative Medicine (CAM)

Abstract

Meaning, expectation, hope, belief… can be seen as alternative explanations for the placebo-effect, as different mechanisms through which the placebo 'works', or as different ways to conceptually approach one underlying phenomenon. In each case, we still have to explain how for instance on the domain of placebogenic pain relief, the psychological, 'immaterial' construct translates into something 'material', such as endorphin release in the brain. This is the old Cartesian problem of mind/brain dualism.

After three decades of almost purely cognitive symbolic theorizing, connectionism came fully back in the 80ies, with in 1986 the landslide double-book by Rumelhart & McClelland "Parallel Distributed Processing" (PDP). The idea is that any concept (thought, feeling, meaning…) is equivalent in the brain to the activation of a network of neurons. Each such network (or pattern) is *distributed* over a large area of neurons. Many patterns can be active simultaneously, in *parallel*. Most or all of the involved neurons contain only sub-conceptual information, the full concept being emergent from the activation of a pattern. Meanwhile, a torrent of cognitive data are compatible with this theory, not opposing cognitive symbolism but complementing it. In the field of Artificial Neural Networks (branch of AI) this has led to many breathtaking realizations.

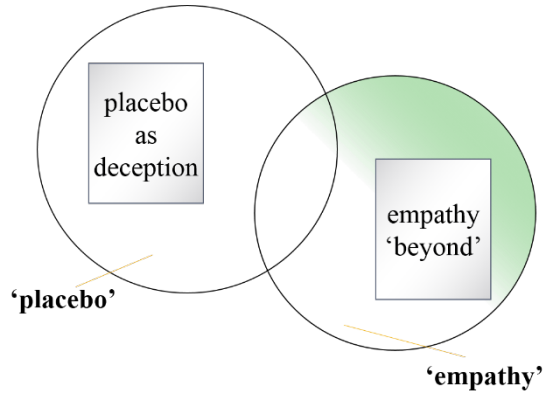
This theory solves the Cartesian problem in that the activation of a pattern is not 'causal to' but indeed *equals* 'having a thought'. A neur(on)al pattern can be seen as

something 'immaterial' and 'material' at the same time. As an analogy, the paint and canvas of a painting are 'all there is' materially seen, yet should not let us forget the art, which is what the painting really is about. *Subconceptual Processing Theory* (SPT) as further development of PDP forms an explanation in one parsimonious sweep of placebo, empathy, consciousness, subconscious mental processing, the etiology of chronic functional pain etc.

Any concrete 'feeling of pain' is an emergent perception that equals the activation of one or more neur(on)al patterns. A suggestion (such as of diminished pain) surrounding an analgesic placebo can be seen as a communication with such patterns. The match at this level is direct. Moreover, one can open up placebo towards this level, making it possible to use the underlying phenomenon of placebo in a direct, rational and overt way in full respect to the patient, as indeed we have done and are further investigating. Hypnosis as another domain that makes heavily use of suggestion, has taught us quite a lot about how to do this. That makes the question whether placebo deception is appropriate, at least partly obsolete. Even more, it shows us that placebo is only one way to 'communicate directly with subconceptual patterns'. It may not be the most efficient, let alone ethical way. Opening up placebo this way brings human warmth, deep meaning and hope in a rational manner back into the center of medicine as a whole.

Difference Placebo – Empathy

In order to avoid confusion, we explicitly distinguish between *placebo* as we see it and *empathy 'beyond the conceptual'* [PLACOM25]. Both are related to 'communication with the subconceptual level' as we will further explain. However there is a huge difference in openness. In our definition of *placebo*, it is always related to deceit, as in the sugar pill that is given as if it were a potent painkiller. Thus: no placebo without deception. Conversely, there is no real 'empathy beyond' without utmost desire for openness. In extremis, placebo and empathy are therefore mutually exclusive. In reality, they can be intermingled, as they also are in most concrete cases, while they readily make each other more difficult to achieve.



For instance, a placebo-pill may be the 'carrier' of empathy in that it may symbolize to the patient the effort of the physician who cares for his patient(s). Conversely, a physician may act in a placebogenic way with little empathy, in that he symbolizes 'cure' for the patient through being knowledgeable, whether this is indeed in reality the case or not. Then again, using empathy as placebo can be felt as paternalistic. Real empathy is 'open' in every respect. This means that it cannot be used for any other purpose. When a physician prescribes a placebo – thus actually lies to his patient – the openness of the relation suffers. Deceit has crept inside. The patient might find out. The physician doesn't see the patient anymore in a natural way.

Placebo, Subconceptual Processing and the Mind-Body Problem

The human brain contains 10^{13} neurons. Each of these cells is alive and continuously active: metabolism, action potentials, synaptic activity… Even when we sleep (or especially then) or are in a coma, dement or neonate, our brain goes on in an incredibly complex way of which the amount of neurons involved only shows the beginning of the real complexity. Yet we are not consciously aware of all this. Actually, we are consciously aware of only very few items at each moment and we can only *become* consciously aware of little of what goes on in the brain.

So how do neurons, as a 'society of neurons,' come to think and even become consciously self-aware? If we take any neuron out of the brain, there is no 'thinking' to be found, no intelligence. On the other hand, if we look at the brain-in-action in a coarse way using fMRI or PET, we see areas becoming active but actually there too we see no individual thoughts or feelings. We can see which (sub)containers in the brain are active in certain circumstances, such as when a person is reacting to a placebo, yet we cannot take a look inside towards 'the thinking process' itself. There is a huge gap between the macro-level and the micro-level. Exploring this gap is

important to know how the placebo-effect comes about. Vice versa, placebo may be useful in showing us more about this gap in that something immaterial (the 'meaning' engendered by an analgesic placebo) enters the system and something material happens (e.g. endorphin release) as a consequence. How is this possible?

Since the 80ies, the domain of 'Parallel Distributed Processing' (PDP) is looking at the thinking process as a process that does not use concepts as smallest relevant constituents, but elements that are smaller than concepts [PLACOM1]. In the brain, these elements may be neurons. This is the subconceptual processing level (SPL) that, as the name says, lies 'beneath concepts'. According to PDP, this subconceptual level is not just a substratum for the conceptual activity at the level higher being implemented in this substratum like software in a computer but is *intrinsically necessary* to much if not all of what thinking is about. The idea is that any concept in mind (thought, feeling, meaning…) is equivalent to the activation of a network of neurons in the brain. Each such network (or pattern) is *distributed* over a large area of neurons and overlaps with other patterns. Many patterns can be active simultaneously, in *parallel*. Most or all of the involved neurons contain only sub-conceptual information, the full concept being emergent from the activation of a pattern [PLACOM1][PLACOM2][PLACOM7][PLACOM10][PLACOM34]. Some characteristics of PDP [PLACOM2] that are congruent with 'the human experience' are enumerated in table 1.

TABLE 1: characteristics of PDP that are congruent with 'the human experience', with placebo-related examples.

- **graceful degradation**: gradual functional decline when a system is damaged or overloaded. *E.g. when attention is distracted from taking the placebo.*
- **multiple 'soft' constraint satisfaction**: multiple constraints compete, whereby the final solution is the one that satisfies most of them. *E.g. when multiple elements heighten / lower placebogenic expectation.*
- **content-addressable memory**: filling in missing pieces of information towards pattern completion. *E.g. when a placebogenic environment is partly recognized from prior experiences.*

- **capacity to spontaneously learn from experience**: increasing appropriateness of the network's responses to a class of inputs. *E.g. conditioning-like learning experiences.*
- **spontaneous generalization**: by means of the same mechanism that recognizes explicitly trained patterns. *E.g. experiencing / seeing medication work, generalizing this towards any medication-placebo.*
- **working with 'exemplars' towards categorizations**. *E.g. after having had one good experience with a medical procedure.*
- **attribution**: making inferences from 'known' properties to other properties. *E.g. knowing that doctors have studied a long time -> "They must know it best."*

Meanwhile, a torrent of cognitive data are compatible with this theory, not opposing cognitive symbolism (i.e. the conceptual level as sufficiently descriptive for many situations) but complementing it. In the field of Artificial Neural Networks (branch of AI) this has also led to many breathtaking realizations [PLACOM35][PLACOM36], such as differentially diagnosing cancer in vaginal smears [PLACOM31].

A neuronal pattern can be seen as something 'immaterial' and 'material' *at the same time (thus no causality)*. This is not materialistic reductionism. As an analogy, the paint and canvas of a painting are 'all there is' materially seen, yet should not let us forget the art, which is what the painting really is about. Brain activity does not generate conscious experience or mental activity in general. Subjective phenomena are not the products of nervous system activity. To say that it does, still amounts to the same problem of *how* brain can generate mind. This problem vanishes with the PDP paradigm. Subconceptual Processing Theory (SPT) as further development of PDP forms an explanation in one parsimonious sweep of placebo, empathy, consciousness, subconscious mental processing, the etiology of chronic functional pain etc. Moreover, it solves the Cartesian problem of mind/brain dualism in that the activation of a neuronal pattern is not 'causal to' but indeed *equals* 'having a thought'.

The Modern Subconscious (1)

> "*Consciousness is a much smaller part of our mental life than we are conscious of, because we cannot be conscious of what we are not conscious of. How simple is that to say; how difficult to appreciate!*" (J. Jaynes 1976) [PLACOM28]

When looking at the world, as I am doing now – writing this text – in your past and you are doing now – reading – in my future, we are consciously aware of some objects in the surroundings. What comes to us however are light waves that reach the retina and are decomposed into a myriad of nerve impulses that look like chaos. These travel to different visual areas in the brain. On its way towards conscious or subconscious 'output', all this chaos-like information undergoes a lot of modulation. It all happens of course in less than a second. Important in this is that a lot of this modulation is meaningful *without us being consciously aware of this modulation*. One can see this for instance in the fact that emotionally significant events are more likely than neutral events to capture conscious visual attention, which necessarily happens *before* they are conscious [PLACOM3]. The conscious 'seeing' part happens somewhere at one of the ends of the 'chain'. It is as if we are looking directly at the world, yet what reaches consciousness has been modulated at least as much by our own meaningful pre-conscious processing as by the objects that we 'see'. How this happens, can by far be best explained by SPT principles of neural pattern recognition and subconceptual processing. Of course we do not have most of what we see in our head first, but we have lots of patterns that are more or less coarse and general. E.g. even if we see a baobab for the first time, we recognize it as a tree. Moreover, we recognize it *spontaneously* as such, without having to analyze its characteristics. There is a spontaneous pattern recognition with little to no consciously felt mental effort involved.

This actually works so well that I have no experience of my brain, but I do have experience of my conscious mind (introspection). It is therefore as if my mind is independent of my brain. My brain is 'transparent'. Conversely, I have experience of things in my environment or body. Looking at them, I generally do not experience my mind. Therefore in this case it is my mind that is 'transparent'. So in my experience either I look at my mind OR at my body. They feel separate. It is precisely *because* subconceptual processing works so well, that it is so difficult to see the one in the other and the other in the one.

Likewise with placebo, of which we will see further on that it can best be explained through SPT. Placebo leads to effects in the brain but its power seems elusive for 2 reasons that we already encountered: 1) the mind-body problematic question: how can an immaterial 'placebo-meaning' cause a material change? 2) It works so well that people do not experience it working as such. We explore a third reason in the next paragraph.

Placebo and the Illusion of Control

A further reason why the subconscious gets a hard time at being acknowledged is that people like to feel in direct conscious control over their own thoughts, feelings and actions. The idea of subconscious 'control' gives a sense of chaos or worse, of being utterly 'un-free'. Over the ages, people have therefore preferred to rather see sources of healing in anything external than in something subconsciously-internal. The external can at least be possibly put under conscious control. If no real cure exists, at least placebos are instruments that give the illusion of control: taking the pill makes us better. We have the taking of the pill under control. This implication is probably the reason why placebo has been overlooked for so long, in favor of all kinds of sometimes *very* weird explanations. "*The history of medical treatment until relatively recently is the history of the placebo effect.*" [PLACOM4]. Presently in the West, we see a renewed success of many CAMs filling the same explanatory void.

Even when confronted with knowledge about placebo, there is a preference to keep the illusion of conscious control intact. The placebo-effect is thus either seen 1) as 'automatic', in a view upon the subconscious as meaning-devoid, or 2) as 'meaningful, therefore a conscious activity'. In 1), it is explained by classical conditioning theory, in which subconscious meaningfulness can rightfully be neglected between input and output. In 2), it is explained by hope/belief/expectancy as consciously controllable.

According to SPT, placebo is essentially a subconceptual processing that is 'meaning'-replete while being autonomous, i.e. not needing conscious control in order to be actively influential in many ways.

The Modern Subconscious (2)

We can now take a look at the relevance of the 'modern' (non-Freudian) subconscious. Actually this view is much older than the Freudian. Although Descartes didn't accept the existence of non-conscious mental activity, others certainly did. E.g. John Norris, 1690: "*There are infinitely more ideas impressed on our minds than we can possibly attend to or perceive.*" Wilhelm Wundt in +/- 1870 believed that mental processes are almost totally unconscious and that we become consciously aware only of the results of these processes. It is our subconscious that continuously creates and produces. Nietzsche too saw fundamental mental activity as subconscious, all knowledge being "the making conscious of the subconscious".

A good definition of the 'modern' subconscious may be: *all mental processes of which we are not conscious yet that influence our thoughts, emotions, perception and behavior in meaningful ways.* As such, the subconscious does almost anything of mental importance. Some examples where we can see the subconscious in action are enumerated in table 2.

TABLE 2: some examples where we can see the subconscious in action:

- cocktail party effect: we suddenly hear our name in a lot of noise [PLACOM5]
- free associations: without knowing where from, the answer is 'suddenly there'. E.g. the Canadian researcher Kenneth Bowers in letting people search for an associated word on basis of 5 clue words [PLACOM6].
- saccadic eye movements [PLACOM7]
- driving a car without conscious awareness, arriving somewhere without remembering anything in between
- mere exposure effect of valuing something more positively also when exposure was subliminal [PLACOM8]
- inattentional blindness: missing something when attention is elsewhere [PLACOM9]
- blindsight patients can meaningfully react to information without their conscious awareness of it [PLACOM10]
- tip of the tongue phenomenon [PLACOM32]

- priming through subconscious associations even with words that are not consciously seen (subliminal) [PLACOM7]
- ideomotoric behavior: representation of a behavior being sufficient for initiating that behavior [PLACOM33]
- the inspiration of an artist or scientist comes without the person himself really knowing how it comes to him. E.g. the famous mathematician H.Poincaré (1854-1912) studied this phenomenon in the 'discovery' of mathematical solutions. He described "*spontaneous and unexpected inspiration as a consequence of prolonged and unmistakably unconscious effort.*" [PLACOM14]
- Recently, fMRI has made it possible to have a new look at mental processing that goes on before conscious awareness. E.g. research by John-Dylan Haynes shows that simple decisions can be traced in the brain up to 10 seconds or more before we consciously become aware of them [PLACOM11][PLACOM12][PLACOM13]. Note that these 10 seconds are not a time lag between brain and mind, but instead between subconscious and conscious processing. The brain and mind are present in both of these, and progress together with no delay between them.
- Double-blind RCT: The '*double'* is needed because the expectation of the physician can, without him consciously knowing so, influence the expectation of the patient.

In view of SPT, there are not 2 separate mental domains, one conscious and the other subconscious. This idea is mainly a Freudian relic. Instead, there is one whole of mental activity, part of which has the additional characteristic of being conscious. This begs the question why. Is it for the sake of consciousness itself or is consciousness a by-product? We can use the metaphor of undersea mountains. The mountains do not rise in order to get above the surface of the sea. Also, when an island is formed, this does not float upon the sea, unrelated to the mountain below. This image shows how consciousness is not just another, additional factor of our brain when compared to other animals. The reason why we have consciousness has to be searched in our subconscious itself. Therefore also we cannot say that placebo has no influence upon the subconscious. If it reaches consciousness, it does so *through* the subconscious. It is not the placebo pill that generates hope or

expectation, but our own subconscious. From here eventually, it may or may not reach consciousness. Of course, once the breakthrough of consciousness arose through evolution, its plentiful advantages gradually emerged. However, these advantages can be seen to result from increasingly complex *subconceptual* processing, from which consciousness came to light as a fortuitous byproduct. In this way, our conscious thoughts are shown to be much more meaningful than they would otherwise be. This does not minimize the importance of conscious thinking – quite the opposite.

Placebo and Change at the Subconceptual Processing Level

One can change one's mind for instance on the basis of logical thinking, experience, authority or 'evidence'. Intuitively, it may seem as if this change is consciously engendered. In reality, one does not *consciously decide* to change one's mind. A sufficient reason to change needs to be present; then, the change itself happens 'spontaneously'. Likewise, a person cannot voluntarily change his expectation (or more generally his 'belief'). A belief comes 'from inside'. I recognize it as 'my' belief, yet it is not in 'my' discretion to simply change it. That is because belief resides in subconceptual patterns [PLACOM7]. These subconceptual patterns of belief are changed by 'evidence'. I cannot consciously stop this change either: when the evidence accrues and I agree with its worth, then my belief changes without my conscious interference. Yet my beliefs feel very much like 'me' and rightfully so. The point is that 'me' is conscious and subconscious in what I regard as 'my' beliefs.

A placebo too, as some kind of (false) 'evidence', can change one's beliefs but it cannot do so directly at the conscious level. A placebo-effect is therefore not the result of a conscious event although it may feel so because of what may be called the 'subconceptual-transparency principle': when the result of subconceptual processing reaches consciousness, it is either just a vague feeling that one cannot put his finger on, or it has already become conceptual. In both cases, the subconceptual is transparent, therefore we may think it doesn't exist.

Likewise I cannot consciously choose what something like a placebo *means* to me. I can encounter for instance something that changes for me the meaning of something else. When I read about an experiment in which university professors with no psychotherapeutic experience get the same psychotherapeutic results as psychotherapists with a lot of experience [PLACOM29], then what psychotherapy

means to me changes in another direction than when the experiment would have had the opposite result. But I cannot consciously *choose* the direction in which what-it-means-to-me changes. It happens spontaneously. What something means to me can change what something else means to me. A changed belief in something can change my belief in something else. These changes happen at the level of subconceptual patterns *without* my conscious volition.

SPL can also be called the 'meaning level'. One can see 'meaning' simply as the way subconceptual patterns can influence other subconceptual patterns. If there is no influence from a pattern, than that pattern has 'no meaning to me'. This is not because it then 'doesn't cause meaning' but because it 'is no meaning'. "What is the meaning of this to me?" is therefore the same question as "How can it influence me?" and as "How can it sub-conceptually change other subconceptual patterns in my mental landscape?" In a stressful situation, not the situation is stressful but what it *means* to me. Once I am in the situation with that meaning, stress comes automatically. A placebo can mean to me the expectation of getting better by influencing overlapping patterns already inside me. However it does so with little sophistication. There is only one message that may even run counter to my own 'nature' that made me feel ill in the first place. When the chronic pain is meaningful, just cutting it out with no further internal change may not be the best way to proceed. Of course, such argument is valid for any painkiller, especially if taken chronically.

Within the framework of SPT, the difference between 'conditioning' and 'expectation modulation' becomes less relevant while the action is seen as always amounting to pattern completion / recognition being inhibited or facilitated even before they start attaining consciousness. When a placebo is repeatedly administered, a natural degrading of the placebo-effect occurs because the patterns are not reinforced. The 'system' starts to learn that what is given, has no active substance. It learns the internally inactive pattern of the placebo itself. This learning process is spontaneous. No rules need to be applied; no discrete elements need to be conceptually recognized. This is an example of spontaneous generalization. E.g. in a study by Fedele et al., the efficacy of placebo as painkiller for menstrual pain diminished from almost equal to a painkiller (NSAID given to a control group), to a drop of 90% over 4 months [PLACOM30]. This conditioning / deconditioning paradigm can be added to the plain giving of information, e.g. that what is given is plain sugar, or maybe an effective painkiller 50% of the time… Also one can without

telling so give sometimes a placebo, sometimes an effective painkiller, through which the drop in effectiveness of the placebo will be less pronounced. There can also be an effect of prior conditioning by an effective painkiller as well as a list of other modulating factors: getting one or 2 placebos, the shape of the placebos, whether they are 'branded' or not, meanings, attributions, desires, imagery, expectations concerning therapeutic modalities, circumstances, condition to be treated, etc. The seamless and consciously effortless integration of all these elements is an example of multiple 'soft' constraint satisfaction typical for neural networks. The end-product is the placebo-effect that one can discern.

As SPT predicts, placebogenic analgesia follows the patterns that are most prone to be activated. E.g. the more recent a person has had experience with the pain diminishing aspect of morphine, the better he will respond to placebo by endorphin pathways. When the same person gets another analgesic before getting the placebo, then the same placebo works in non-endorphin ways [PLACOM37]. These patterns cannot be chosen at all through conscious means.

Placebo, Subconceptual Processing and Western Modern Medicine

Placebo is embarrassing to Western modern medicine since it is a reminder of its persistent dualism. Western modern medicine has only recently (+/- 200 yrs) come out of the swamp of pre-scientific 'magical' thinking. Therefore there is an additional urge to focus upon the molecular level which gives a very magic-clean impression. At the same time however, and very contradictory, the same molecule-minded individual researchers frequently see 'the normal mind' as totally apart from the brain. The whole 'placebo thing' has no place in this. It is seen as discardable 'noise'. Moreover, placebo shows that much of 'healing' is done by the patient himself, through means for which – apart from truly underrated empathy – in principle no doctor is needed, except the 'doctor as placebo' himself, which de facto makes him again somehow the shaman of bygone ages.

This is not only about 'pure placebo' but about placebo as part of any medication and any medical encounter. Even more, when a real medication is given, with effect and side-effects, this kindles patterns within the patient's mind that thereby can be completed much more easily. The medical effect acts as a primer of these patterns. The side-effects too initiate a pattern of "something happens that will make me better". A pattern kindled like this, can become completed more easily through the

expectation engendered by environmental factors. Thus medication enhances placebo. We do not readily notice this in double-blind studies since of course the medication-enhanced placebo-effect is present in the medication arm and not in the placebo arm. A simple subtraction of the results in the two arms makes us look right over it.

Medical rationalization has increased over the decades of the 20th century. No 'magic' is allowed anymore. The physician has evolved from practitioner to clinician, scientist, technician, trying to get rid of shamanism. Yet placebo shows that the latter has by far not yet left the picture of scientific medicine itself. In addition to this, in medicine's attempt to get 'magic' out, people go to CAM in search of it. People need what 'magic' apparently gives them, however according to us they do NOT need 'magic' as a sham if what-lies-behind-it (SPL) can be brought to them in a truly rational way. This is the huge responsibility of Western modern medicine. We have to look at 'the beast' in order to be able to transform it. In a way, placebo-as-deceit provides a full picture upon that what needs to be transformed. Scientifically speaking: we need better ways to realize subconceptual communication for the sake of all patients with chronic pain, depression, psychosomatics, addictions etc.

Ancient Far-Eastern Insights Run Parallel to Modern Western Insights

The term 'Zen-Buddhism' is popularly known in the West. However, Japan didn't invent most basics in this, but was inspired by an older civilization: China. The term 'Zen' comes from the Chinese 'Chan', which comes from the Sanskrit 'Dhyana', which simply means 'meditation'. We focus this chapter upon Chan, a Mahayana form of Buddhism adapted to the Chinese mind (+/- from 6th century onwards) together with being thoroughly integrated with the then already prevalent Daoism [PLACOM15]. It is/was a very strong tradition with many great thinkers and a lot of people investing their lives in order to attain 'enlightenment'.

Eastern 'enlightenment' (not to be confused with the Western 'Era of Enlightenment') is sometimes confused with 'nirvana', which is literally 'that what remains when the candle light is blown out': a state without striving towards anything at all, therefore also without 'dhukha' or (badly translated by necessity) something like 'frustration'. Typical for Mahayana is that it radically places enlightenment above personal nirvana. For our purpose, the concept <enlightenment> is specifically important because of its parallel with Subconceptual

Processing. This way, ancient East and modern West come together in a unified view upon human depth. We can probably best explain this through 2 related Eastern concepts:

- 'prajna' (enlightened wisdom): which is actually 2 words, being 'pra' and 'jna'. 'Pra' is related to our 'pre' and can also mean 'premium'. 'Jna' means 'thinking'. In other words the subconceptual processing that goes on before something conceptually appears in consciousness. Prajna denotes the ability of communication with the subconceptual level as well as its realization in real-life. For instance, we know that 'pain' is a feeling that is the end result of a lot of SPL-interpretation and modulation of some awareness that precedes 'pain'. By gently getting access to the SPL-level, one can understand one's pain better, thereby also where it comes from and what it actually *means*. Understanding one's own pain, one can also better understand the pain of others, help them get closer to their meaning level and change 'from inside out' (empathy beyond the conceptual [PLACOM25]).
- 'emptiness': not to be confused with sheer emptiness, being nothing at all. 'Emptiness' is empty of denotable things. Scientifically speaking, it is empty of concepts, however full of 'potential', this is: patterns that may or may not 'crystallize into concepts'. Thinking without concepts refers directly to the subconceptual level or what we may call the modern subconscious.

'Enlightenment' can be an experience or a state. One can see in it a 'going beyond' the conceptual level, not therefore by leaving this level but by not letting it stand in the way of what we might call 'deepest intuition'. The Chan idea of enlightenment, also called 'non-dualistic thinking' is an urge towards integrating the subconceptual level in one's thoughts and feelings (as experiences) and eventually whole life (as state) to a huge degree, with formal meditation as a main exercise towards that. Note that this is certainly not being free of thinking at all. With little burden by conceptualization however, subconceptual patterns are free to float, make new associations, come to new insights, consciously or subconsciously. This is also related to perception in general. When one looks at a tree in a non-dualistic way, one is not looking at 'this element of a broad set of trees that one knows through the concept <tree>', but to this tree that one can only see through oneself, with an awareness almost as of looking at oneself unified with the tree. Non-dualistic = sub-

conceptual. This is a much more 'intimate' view, one might say, than when one immediately recognizes a 'tree' conceptually.

In Mahayana, the purpose is to relieve others' suffering (dhukha). In Chan in particular, the focus is on the relationship with other people. The bodhisattva as one who dedicates his life to enlightenment is present at the market place, relating to 'all sentient beings' in an enlightened, therefore also compassionate way. The ultimate ideal is to just 'say the right word at the right time', so as to guide others to have the same experience. The mythical Buddhist Bodhisattva of Compassion is in the Chan tradition also called '(s)he who hears the suffering of the world', not only conceptually but foremost in a deeply subconceptual way, thereby being 'deeply intimate' with people or even all sentient beings who want to be heard. One may rightfully recognize in this the *nonspecific factor of psychotherapy* which we in the West call empathy. This is not the 'empathy' of the one who stays at the conceptual level but of the one who develops 'empathy beyond' [PLACOM25]. According to a lot of Western research, this seems to be thé key factor that is really 'healing' in any client-therapist relationship. One may notice that this sharply contrasts with the multitude of underlying theories and methodologies of Western psychotherapies that are almost all precisely very concept-based. We can learn a lot from ancient East.

Subconceptual Processing and Chronic Functional Pain

According to SPT, stimuli from the periphery continuously reach the brain and start activating a number of patterns (different patterns in different areas as are active at neuro-imaging). Together with a lot of other input to the same sets of neurons, this modulates the activation of a number of emerging subconceptual patterns (multiple constraint satisfaction). These emerging patterns strive towards self-completion, part of which means the downplay of other patterns. In the end (after some 100s of milliseconds), one pattern gets enough momentum towards completion so as to become stable. The winner takes it all, at least consciously. Subconsciously, the losing patterns have influences in many ways, as well as work together with the winner in order to flow into a ride towards the next winner. In this, each ride again can be likened to reaching a local minimum in a neural landscape. If the pattern at that minimum has a pain-related meaning, the activation of that pattern and of other patterns that may directly be activated by this pattern, is equal to the feeling of pain. Note again that it does not 'cause' but 'is' this feeling. The characteristics of

this pain as can be investigated with the use of for instance the McGill Pain Questionnaire (MPQ) are realized through a host of related patterns that contribute to the overall experience, either causally or consequentially or as an intrinsic part of the whole.

Part of the pain experience involves the (inhibition of) secretion of neurotransmitters. As explained earlier, it is not the (secretion of) any neurotransmitter that equals the feeling of pain. E.g. endorphins are a group of related neurotransmitters that are definitely involved in pain modulation. The body (nature, evolution) chooses this more or less exclusive role for a group of neurotransmitters probably in order to be able to influence internally, through one molecular mechanism, a whole dimension of feeling / behavior. 'Pain' can be seen as one of the most important states an organism can be in, potentially being life-saving through its modulation of attention towards certain things that need direct attention, as well as signaling aversion. It is opportune for the organism to be able to modulate its pain state in one go and rather quickly. Through modulating endorphin concentrations over a whole domain of potential neural networks, it achieves this goal. Note that looked at it this way, the endorphin release is by itself not the end stage of an internal analgesic response, but serves to influence neural networks which can be seen as the end stage. When morphine (or placebo) acts on cells / synapses, its action gets a pain-related meaning only because these cells form parts of networks. As an analogy, the individual cells are like tiny parts of letters of a text. The tiny parts are data but they do not carry information by themselves. The information (meaning) only exists at quite higher levels. By inhibiting the tiny parts to form larger patterns – such as through morphine – the meaning of these patterns gets lost. However this does not reach these patterns at their own level. The action of morphine is thus not constructive but destructive. If chronically taken, we can foresee and also see side-effects through this, described as 'the opioid downhill spiral' [PLACOM16].

When we have an acute pain, impulses go from the periphery to the brain and are recognized as 'pain'. At least, this is part of the picture. Even with acute pain, the brain is much more active in 'parallel and distributed ways' than as a simple receptor of peripheral information. In the case of chronic pain, the brain is even more involved as such. E.g. phantom pain: pain in a body part that is not there. This way of course, any chronic pain can be seen as phantom pain, whether the body part is there or not. The brain itself creates the pattern of 'pain in the bowels'. Sensory

information coming from the bowels is then interpreted within this pattern… as pain. To another person, the same information might be interpreted as neutral or even a pleasant feeling of distention. To the person with IBS, it is pain. This explains how changes in the end organ (more or less distention) can be felt as painful stimuli, thereby heightening the idea that 'something must be wrong down there'. This makes those individuals reluctant of the contention that it would be 'all in the head'. They – rightfully and wrongfully at the same time – just feel that it isn't.

Hyperalgesia syndrome may be seen as a state in which pain-patterns are more likely to become fully activated. They are made activation-prone, by being for instance constantly and partially (subliminally) activated. Thereby this person more quickly feels 'pain'. The so-called pain-threshold is lowered. These patterns may become even stronger through repeated cycles of pain, which results in a vicious circle and full-blown hyperalgesia. It is thought that hypersensitivity plays a key role in any case of CFP [PLACOM17][PLACOM18], therefore not the chronic input of pain-information from the periphery. This does not explain however, the role of CFP itself.

CFP syndromes can be seen as one syndrome with diverse appearances. The unification can be traced into the brain. Here we see a network of macro-level areas (Melzack's 'neurosignature') acting together. These areas are not correlated with singular meaningful patterns. Within these areas, we see neurons, synapses. These are also not correlated one on one with singular meanings. Yet we know meanings are important in the development of chronic pain at many levels and many points in the processing chain. The most likely candidates to realize these singular meanings are subconceptual neuronal patterns. This way the communication of placebo to chronic pain is direct: patterns communicate to patterns. Recall that these patterns are mind as well as body, depending on the way one looks upon them. Medication cannot influence the SPL in a meaningful way. The molecular area that we see being influenced by medication is almost exclusively the synapse. It might be that in chronic functional pain there are synaptic disturbances that are normalized through the medication. It is however more probable that painkillers do not 'right the wrong' at this level, but rather undo nature's natural processes.

Even more encompassing than the unification of CFP syndromes, {chronic physical pain / chronic existential pain / depression} can be seen as one entity [PLACOM19] that may temporarily withdraw the animal from activity when a prolonged time for reorientation is asked for, this is: not in the order of minutes but days or weeks. An internal change may be needed that takes this time. However, when a human,

through means not available to most other animals, resists this change, a vicious circle may start that eventually transforms a condition with a natural purpose into a condition that more and more resembles a disease. According to circumstances, this may be a depression, a chronic pain syndrome or another kind of psychosomatic suffering. In SPT-terminology: patterns that are at the same time urged as well as resisted to be realized are driven more and more into a realization that feels like pain. This too is a kind of 'hypersensitivity': what to one person feels as no-pain, to another more and more feels like chronic or recurrent pain, depression… This way, the most important 'cause' in the causal landscape that leads to the ensuing syndrome, may lie in the resistance against the realization of the neural patterns. In short: if they cannot be realized in a good way, more and more they gain momentum and become realized in a bad way.

Subconceptual Communication Beyond Placebo

Clark Hull, one of the generally acknowledged founding fathers of modern hypnosis, already wrote in 1933: "*The only thing which characterizes hypnosis as such and which gives any justification for calling it a 'state' is its generalized hypersuggestibility… The difference between the hypnotic and normal state is therefore quantitative rather than qualitative. No phenomenon whatsoever can be produced in hypnosis that cannot be produced to lesser degrees by suggestions given in the normal waking condition.*" [PLACOM20, p.391] This finding has been replicated over the next decennia until now in studies with increasingly refined methodology [PLACOM22]. As an example of this, Milling et al. compared hypnotic and nonhypnotic suggestions upon pain reduction [N=60], finding no significant difference. Both were equally more effective than a no-treatment control condition [PLACOM21]. Kirsch et al. have studied more than 75 years of hypnotic research and concluded that "*1) all of the phenomena produced in hypnosis by suggestion also can be produced by suggestion without the induction of hypnosis, 2) the induction of hypnosis produces a relatively small increase in responsiveness to suggestion, and 3) hypnotic and waking suggestion are highly correlated.*" [PLACOM22] In other words, it is suggestion that produces the effects. As a modern critique, Rainville et al. point out that in view of neuroimaging results, one can say there is a "*neurobiological basis of hypnosis, demonstrating specific patterns of cerebral activation associated with the hypnotic state.*" [PLACOM23, p.110] But this is circular reasoning. *Never* can neuroimaging prove any distinction between hypnotic suggestion and suggestion

alone to be more than a distinction by convention… since this too would only be a matter of convention. As Kirsch et al. note: "*If suggestion and the induction of hypnosis are confounded in the design, even the most sophisticated neuroimaging results cannot be interpreted as evidence of hypnosis.*" [PLACOM24]

One may call *hypnosis* that what is measured on a scale of hypnotizability (this is: response to suggestions after a hypnotic induction). However, such a scale only measures the degree to which one conforms to the scale. If the scale is presented as hypnotic, then it measures the degree to which people can respond to a situation that is thus presented as hypnotic, such as in a possible subsequent laboratory situation. This is confirmed by research on the domain of pain [PLACOM27]. As Spanos et al. point out, imaginative analgesia suggestions are differentially effective for 'highly hypnotizable subjects' only because response to such suggestions involves the same expectancies and imaginative abilities required for responding favorably to the test items. In the opposite direction but equally important, inviting subjects to use imaginative suggestions (such as through preceding the pain-test with a standardized hypnotizability test) may be an implicit injunction *against* using non-imaginative coping strategies, which 'weakly hypnotizable subjects' may prefer [PLACOM27], thus making the test itself a cause for conformation to the test. Moreover and not surprisingly, the best predictor for hypnotic suggestibility turns out to be non-hypnotic imaginative suggestibility [PLACOM20]. Even Weitzenhoffer, who co-authored the Stanford Hypnotic Susceptibility Scale, argued that scales such as this do not really measure hypnotizability, but rather imaginative suggestibility [PLACOM22].

At the other side, the placebo itself being inert, what is active is the accompanying suggestion, the meaningful message it communicates at the subconceptual level: 'subconceptual communication' of which 'verbal suggestion' is only one way to attain it. Indeed, for placebo and hypnosis alike there is no reasonable doubt that broadly seen, in their mode of administration there is anything but suggestion. In other words, suggestion is their common language, be it that the way this language is spoken, what is said and what is perceived by the patient may be very different. Hypnotic induction and hypnotic suggestions as vehicles consist of nothing but suggestion. A placebo too, be it a pill or a surgical procedure or whatever, as well as what is said by the clinician about this pill or procedure, consists of nothing but suggestion. Without suggestion, one could not even start with a hypnotic induction, nor would the placebo pill be anything more than plain sugar. Placebo and hypnosis

are still frequently seen as very different phenomena, but in view of SPT, they are two ways of subconceptual communication. Moreover, the idea of trance may itself mainly be a placebo. The difference between 'hypnotic suggestibility' and 'placebo suggestibility' that is frequently pointed out as argument that they are different phenomena, is probably no more than a measure of confounders such as the degree to which a subject is susceptible for 'things touchable' versus 'things untouchable'.

According to SPT and many researchers within the field of hypnosis itself, in-depth suggestion can be brought without trance. We therefore have here a direct means to bring the 'placebo-effect without placebo'. Moreover the term *hypnosis* brings to many people connotations of for instance mechanically changing the subconscious. We therefore posit for the trance-less and further connotation-less use of suggestion the term 'autosuggestion' to put emphasis on the fact that the client/patient is central in this in every respect while getting support when needed [PLACOM26]. Furthermore, we think that autosuggestion needs to be brought in very ethical ways, for which we deem necessary a combination of openness, freedom, depth, respect and trustworthiness. Note that 'empathy beyond' in our view naturally combines these characteristics, while placebo-as-deceit as we defined it in this text has none of them. We therefore think that an ethical and rational way to go forward in bringing subconceptual communication into healthcare, thereby also bringing human warmth, deep meaning and hope in a completely rational manner, is a proper combination of 'empathy beyond' and autosuggestion.

Conclusions

The placebo-effect can best be understood at the subconceptual processing level. This way also the similarity as well as the difference with empathy can be fully explored. To many, the mind-body problem and subconceptual-transparency principle play a huge role in making it difficult to accept the power of placebo. Moreover, to fully make use of it in an open way, it will be needed to transcend the illusion of conscious control that placebo-as-deception provides.

Within Chan, Eastern thinking has developed in a way that is compatible with modern Western insights in subconceptual processing. We may find in it a rich source of information and wisdom. Another source is the domain of hypnotic suggestion insomuch as it has gotten rid of connotations from classical hypnosis. In

an open way, we can see subconceptual communication or (auto)suggestion as the tool that can for always make placebo-as-deception unnecessary and open the power of subconceptual processing & communication, that the placebo-effect is only part of, to a huge number of medical problems that do not and even possibly just cannot get proper solutions with present-day means. However for this to happen, medicine will have to change profoundly.

References

[PLACOM1] Rumelhart D.E., McClelland J.L. Parallel Distributed Processing. Cambridge: MIT Press, 1986 (2 volumes)

[PLACOM2] Bechtel W., Abrahamsen A. Connectionism and the mind. Oxford UK: Blackwell Publishers, 1994: 349

[PLACOM3] Niedenthal P., Kitayama S. (Ed.) The Heart's Eye. San Diego: Academic Press, 1994: 289

[PLACOM4] A.K.Shapiro, E.Shapiro The Powerful Placebo. Baltimore: The Johns Hopkins University press, 1997: 280

[PLACOM5] Moray N. 1950 Attention in dichotic listening: affective cues and the influence of instructions. Quarterly Journal of Experimental Psychology. 1950;11:56-60

[PLACOM6] Bowers K.S., Regehr G, Balthazard C, Parker K. Intuition in the context of discovery. Cognitive psychology. 1990;22:72-110

[PLACOM7] P.S.Churchland Brain-Wise, Studies in Neurophilosophy: MIT Press, 2002: 471

[PLACOM8] Bornstein R.F. (1992) "Subliminal mere exposure effects" in Bornstein R.F., Pittman T.S. (ed) Perception without awareness: cognitive, clinical and social perspectives. New York:Guilford: 191-210.

[PLACOM9] Simon D.J., Chabris C.F. Gorillas in our midst: sustained inattentional blindness for dynamic events. Perception 1999;28:1059-1074

[PLACOM10] Gazzaniga M.S. (ed.) Cognitive Neuroscience: MIT Press, 2009: 1294.

[PLACOM11] Bode S, He AH, Soon CS, Trampel R, Turner R, Haynes JD. Tracking the unconscious generation of free decisions using ultra-high field fMRI. PLoS One. 2011;6(6):e21612

[PLACOM12] Soon CS, Brass M, Heinze HJ, Haynes JD. Unconscious determinants of free decisions in the human brain. Nat Neurosci. 2008;11(5):543-5.

[PLACOM13] Haynes JD, Rees G. Predicting the stream of consciousness from activity in human visual cortex. Curr Biol. 2005;26;15(14):1301-7.

[PLACOM14] Ghiselin B. The creative process. New York: New American Library 1952:37-40

[PLACOM15] P.D.Hershock Chan Buddhism Honolulu: University of Hawai'I Press, 2005: 173

[PLACOM16] Schofferman J. Long-term use of opioid analgesics for the treatment of chronic pain of non-malignant origin. J Pain Symptom Manage 1993;8:279–88.

[PLACOM17] Turk DC. Understanding pain sufferers: the role of cognitive processes. Spine J. 2004 Jan-Feb;4(1):1-7.

[PLACOM18] Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: a population study. Pain. 2006;123(1-2):19-27.

[PLACOM19] E.A.Mayer, M.C.Bushnell eds. Functional Pain Syndromes: IASP Press, 2009: 580

[PLACOM20] Hull, C. L. (1933). Hypnosis and suggestibility: An experimental approach. New York: Appleton-Century Crofts

[PLACOM21] Milling LS, Kirsch I, Allen GJ, Reutenauer EL. The effects of hypnotic and nonhypnotic imaginative suggestion on pain. Ann Behav Med. 2005;29(2):116-27.

[PLACOM22] Kirsch I, Mazzoni G, Montgomery GH. Remembrance of hypnosis past. Am J Clin Hypn. 2007;49(3): 171-8

[PLACOM23] P. . Rainville, R.K. Hofbauer, T. Paus, G.H. Duncan, M.C. Bushnell and D.D. Price Cerebral Mechanisms of Hypnotic Induction and Suggestion J Cogn Neurosci. 1999;11(1): 110-25

[PLACOM24] Kirsch I, Mazzoni G, Montgomery GH. Hypnotic history: a reply to critics. Am J Clin Hypn. 2007;49(4): 249-54.

[PLACOM25] Mommaerts JL, Goubert L, Devroey D. Empathy Beyond the Conceptual Level. Perspectives in Biology & Medicine. 2012b (Accepted).

[PLACOM26] Mommaerts JL, Devroey D. The placebo effect: how the subconscious fits in. Perspectives in Biology & Medicine. 2012a;55(1):43-58.

[PLACOM27] Spanos NP, McNeil C, Gwynn MI, Stam HJ. Effects of suggestion and distraction on reported pain in subjects high and low on hypnotic susceptibility. J Abnorm Psychol. 1984;93(3):277-84.

[PLACOM28] J. Jaynes 1976; The Origin of Consciousness in the Breakdown of the Bicameral Mind. Boston: Houghton Mifflin (p.23)

[PLACOM29] Strupp HH, Hadley SW. Specific vs nonspecific factors in psychotherapy. A controlled study of outcome. Arch Gen Psychiatry. 1979;36(10):1125-36.

[PLACOM30] Fedele L, Marchini M, Acaia B, Garagiola U, Tiengo M. Dynamics and significance of placebo response in primary dysmenorrhea. Pain. 1989;36(1):43-7.

[PLACOM31] Dounias G, Bjerregaard B, Jantzen J, Tsakonas A, Ampazis N, Panagi G, Panourgias E. Automated identification of cancerous smears using various competitive intelligent techniques. Oncol Rep. 2006;15 Spec no.:1001-6.

[PLACOM32] Cleary AM. Relating familiarity-based recognition and the tip-of-the-tongue phenomenon: detecting a word's recency in the absence of access to the word. Mem Cognit. 2006;34(4):804-16.

[PLACOM33] Wegner D.M. The illusion of conscious will. Cambridge: MIT Press 2002

[PLACOM34] Churchland P.S., Sejnowski T.J. The Computational Brain. The MIT Press, 1992: 544

[PLACOM35] Rabunal J.R., Dorado J. (eds.) Artificial Neural Networks in Real-life Applications. Hersey Information Science Publishing,2005:300

[PLACOM36] Tosh CR, Ruxton GD (Eds) Modelling Perception with Artificial Neural Networks Cambridge: Cambridge University Press,2010: 408

[PLACOM37] Amanzio M., Benedetti, F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific sub-systems. J Neurosci. 2006;19:484–494.

4.19 LETTER TO EDITOR: It's Too Soon to Recommend Probiotics for Colic.

(commentary to: Pediatrics. 2010 Sep;126(3):e526-33.)

Jean-Luc Mommaerts, M.D., M.Sc., Dirk Devroey, M.D., Ph.D.

J Fam Pract. 2011;60:251-252.

The authors of "Colicky baby? Here's a surprising remedy" (PURLs, J Fam Pract. 2011;60:34-36) suggest that probiotics are a remedy for infantile colic. The study was funded by producers of probiotics, but the rigorous study design is deemed to make bias unlikely, leading the authors to recommend a change in practice. We very much hope this will be a big step forward, but feel the need to air our concerns: namely, that probiotics (cost: about $40 per month) may substitute for parental love (cost: $0 per lifetime). It's a huge marketing opportunity, as 10% to 25% of infants have infantile colic.[1] We are not fully convinced of the benefits.

To start with, the term "infantile colic" suggests an abdominal cause, although this "cause" is not mentioned in published criteria.[2] It has been suggested that infantile colic may simply lie at the upper end of a normal distribution.[3]

Related to the treatment, no adverse events were reported, nor any differences between the placebo and probiotics groups in frequency of stools or incidence of regurgitation or constipation.

Then why did the babies cry less? The answer seems obvious: because they have less pain. But why do babies have less pain from having an enhanced intestinal flora vs a natural one, while having no change in gastrointestinal functions? Has nature gone astray? Could there have been factors that made mothers feel the difference between the treatment and the placebo groups, such as side effects that were not reported and that may have enhanced the placebo effect? (Notably, one study found a substantial placebo effect on colic.[4]) Babies are extremely emotionally symbiotic with their mothers, and thereby very prone to "suggestivity" coming from the mother (or father).

We certainly do not mean to suggest that colic is related to poor parenting skills. We do, however, see a need for more investigations before turning the prescription of probiotics for infantile colic into a clinical guideline.

REFERENCES

1. Roberts DM, Ostapchuk M, O'Brien JG. Infantile colic. Am Fam Physician. 2004;70:735-740.

2. Hyman PE, Milla PJ, Benninga MA, et al. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2006;130:1519-1526.

3. Savino F, Cordisco L, Tarasco V, et al. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatrics. 2010;126:e526-e533.

4. Metcalf TJ, Irons TG, Sher LD, et al. Simethicone in the treatment of infant colic: a randomized, placebo-controlled multicenter trial. Pediatrics. 1994;94:29-34.

4.20 LETTER TO EDITOR: Acupuncture for Dyspnea on Exertion in Chronic Obstructive Pulmonary Disease: no Blindness

(*Commentary to: "*A Randomized, Placebo-Controlled Trial of Acupuncture in Patients With Chronic Obstructive Pulmonary Disease (COPD)")

Jean-Luc Mommaerts, M.D., M.Sc., Jan Vandevoorde, M.D., Ph.D., Dirk Devroey, M.D., Ph.D.

Arch Intern Med. 2012;172(22):1772-1773.

Suzuki et al [1] claim that their placebo-controlled trial of acupuncture clearly demonstrates that this is a useful adjunctive therapy in reducing dyspnea on exertion in patients with chronic obstructive pulmonary disease. They used a design in which a placebo acupuncture group (PAG) received treatment with a Park sham device "with a guide tube mounted on a base adherent to the skin. The tips of the placebo needles used for the PAG were blunt and appeared to be penetrating the skin but actually telescoped back into place." [1, p.880] With no blinding of the practitioner, the authors assessed subjects' blindness after the study, letting subjects choose between "real acupuncture," "placebo acupuncture," and "don't know." Of the real acupuncture group (RAG), 25 of 30 subjects reported "don't know." Of the PAG, 26 of 32 subjects did so.

"Blindness" in this regard depends on what "don't know" means: does it mean "I have no clue" or "I am not 100% sure"? In the former case, blindness is very high, while in the latter case, very low. An additional forced choice and/or asking subjects to indicate their degree of doubt would have brought us closer to this vital information.

The authors say that "for the RAG patients, needles . . . were manually rotated clockwise and counterclockwise for 3 to 4 minutes at each point during a 50-minute treatment period" resulting in "[p]erception of de qi . . . during insertion and/or manipulation was confirmed at every point in the RAG," while "in PAG . . . no sensation like de qi was reported." [1, p880] They do not say to what degree this was true for each subject or even for each procedure, repeated weekly for 12 weeks. With frequent "sensation of de qi," blindness was virtually nonexistent.

In addition, up to 10 subjects in the RAG vs 0 in the PAG had subcutaneous hemorrhage or needle site pain, strongly diminishing blindness. A possible explanation for the high number of “don’t know” responses may be because subjects said “don’t know” because they did not want to be wrong. In addition, because placebo is a subconceptual phenomenon,[2] even subconscious “knowing” may have a substantial influence on outcomes.

Briefly, we see this study as hardly being a singleblind trial. As a result, this is probably another indication of the power of the placebo itself.[3] Because such studies get referred to in the lay press with the terms blindness, placebo controlled, clearly demonstrates, and acupuncture—and eventually influencing decision takers—we find the combination of these terms inopportune without there being more effort to ensure and assess blindness.

1. Suzuki M, Muro S, Ando Y, et al. A randomized, placebo-controlled trial of acupuncture in patients with chronic obstructive pulmonary disease (COPD): the COPD-acupuncture trial (CAT). Arch Intern Med. 2012;172(11):878-886.

2. Mommaerts JL, Devroey D. The placebo effect: how the subconscious fits in. Perspect Biol Med. 2012;55(1):43-58.

3. Shapiro AK, Shapiro E. The Powerful Placebo. Baltimore, MD: Johns Hopkins University Press; 1997.

4.21 LETTER TO EDITOR: Acupuncture for IVF: Do Not Let Needles Stand in the Way of Empathy.

(Commentary to: "Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: a systematic review and meta-analysis.")

Jean-Luc Mommaerts, M.D., M.Sc., Dirk Devroey, M.D., Ph.D.

Fertil Steril. 2012;97(5): e26.

Zheng et al [1] claim in their meta-analysis that there is no significant difference between acupuncture and placebo when it comes to live birth rates among women undergoing in vitro fertilization because the Streitberger procedure, in which needles do not enter the skin and which was used as placebo acupuncture, appears to be more effective than acupuncture itself. This might be interpreted as a recommendation to choose the Streitberger procedure over acupuncture as the active treatment. The authors seem to agree, saying "…the harmful reaction produced by real acupuncture can be avoided by this noninvasive stimulation…".

We do not share this implied recommendation, because nothing in this article distinguishes the direct effect of acupuncture from the effect of the broad psychologic/social/cultural environment in which it is performed. The authors use the term 'acupuncture' without making this distinction. Is acupuncture something that could be performed by a robot on robot-like participants with no deeper meaning involved? Acupuncture probably means much more than that to the authors, as it does to us.

The authors claim that the Streitberger procedure is not a valid placebo, but using comparable reasoning, it may be that acupuncture can be equally active only through a placebo effect. Assuming that everything that works is not itself a placebo leaves acupuncture unprovable, therefore not proven unless by rational means. This reasoning suggests that all treatments may be placebo. Acupuncture has many characteristics that could lead to a placebo effect, such as invasion of the integrity of the skin, having an aura of ancient wisdom as did bloodletting for 1,600 years in the West, being exotic in the West and homemade in China, displaying strange-looking images of meridians through which the ephemeral life energy Qi might flow,

etc. We only wish to say that this is a very placebo-prone procedure about which the authors strive to point out that there is no positive proof compared with a satisfactory placebo.

We think it is worth spending research resources investigating the exact nature of Qi. We understand the deep importance of Qi in Chinese culture. However, to bring it by way of metal needles in a materialistic manner truly denigrates it, as is mainly done nowadays in the West. In the end, choosing empathy and inner human strength, a part of subconceptual processing, which is to us the real Qi, instead of placeboprone cold needles is a matter of self-respect.

The Streitberger procedure proves to us that the power of placebo, in a broad sense, extends to the domain of fertility. More research is needed. Also, we fear that the idea of acupuncture, implying something outside oneself, stands in the way of inner strength, which is something inside oneself. The feeling of helplessness is one of the most important causes of functional disorders. This might eventually even influence fertility in a negative way. This, too, should be an object of research.

[1] Zheng CH, Huang GY, Zhang MM, Wang W. Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: a systematic review and meta-analysis. Fertil Steril. 2012 Jan 11. [Epub ahead of print]

5 Discussion 1: Subconceptual Processing in a Neur(on)al Network

5.1 The Brain Has 10^{11} Neurons

The study of Artificial Neural Networks (ANN) has led to the development of theoretical neural network models. In this branch of AI, the entities programmed into a computer are tiny, modular nodes with little functionality and a simple interface to each other. The apparent power of an ANN derives from these thousands or millions of nodes working together in cooperation.

One can view human neurons and synapses as being the nodes in an ANN, with the 'neural' network in this case being a 'neuronal' network. Information is stored in this network as highly distributed, massively overlapping patterns of nodes.

When the majority of nodes within a single pattern are simultaneously in an 'active' state, the pattern itself and the information it contains becomes 'activated'. If the pattern is not activated, it still exists in a 'potential' state by virtue of the way the nodes are connected to each other. In addition to this, there are also several other interesting similarities between neural networks and the way that the mind/brain functions.

SEE ALSO ARTICLE: “CLOUD OR CLOCK: IMPLICATIONS OF THE SUBCONSCIOUS ON PLACEBO, DOUBLE-BLIND STUDIES AND MEDICINE IN GENERAL”

The human brain contains approximately 10^{11} neurons, with each neuron having on average some 1000 synapses each of which is a complex and active interface with another neuron. Within the neural network paradigm, each synapse acts as a node, resulting in a breathtaking 10^{14} nodes – each of which is far more complex than an artificial ANN node in a computer. This enormous 'neuronal network' can contain an almost infinite number of patterns, some of which are small and some of which are large and broadly distributed. Some of these patterns are very easy to activate, whereas others are difficult to activate or only activate weakly. By analogy with neural networks, these patterns can be referred to as 'subconceptual patterns'. The concepts they contain are 'virtual' unless the pattern becomes activated due to its nodes being activated (Smolensky, 1988). The subconscious can be seen as the interaction of patterns that are not sufficiently activated to reach the level of consciousness. Subconceptual Communication ('autosuggestion') indicates that it is possible to communicate with these patterns without them being fully activated. In other words, the communication itself has a subconceptual quality giving rise to a feeling of spontaneity.

The *pain neuromatrix* of Melzack's conceptualization can be seen as a network of such neuronal networks. Pain itself, according to this conceptualization, is the result of a communication of 'change' from the periphery of the body to this network (Melzack & Wall, 2008). Analgesic suggestions 'work' because they communicate positive 'change' to this network.

SEE ALSO CONGRESS ENTRY: "PLACEBO AS COMMUNICATION TO NEUR(ON)AL NETWORKS IN CHRONIC FUNCTIONAL PAIN"

One central assumption of cognitive neuroscience is that "for every mental process M, there is a process N in the brain, such that M = N." (Bunge, 2007) Amongst other things, this explains the age-old problem of 'qualia' or 'secondary properties' such as color, smell, loudness and taste. Physical objects do not possess 'qualia', but instead only have primary properties such as energy and velocity. Qualia originate in the brain, and result from the way we perceive primary properties with our senses, and ultimately with our brain – they are mind/brain properties. Furthermore, they are 'emergent' properties, properties that emerge from systems

such as the brain as a whole but which do not exist within individual components such as neurons.

Such emergence is fundamental to neural networks. When we talk about emerged properties in the context of the mind, we refer to this as psychology. On the other hand, the underlying mechanisms we refer to as 'brain science'. Mental processes, such as using language, invention, or experiencing love or pain are *emerged* processes, which we are only conscious of when it is important or worthwhile for us to do so. The processing which underlies these phenomena, such as consciously felt pain, lies primarily in the subconscious neuronal network. At this subconscious level, it is exposed to a wide array of meaning-related influences which, taken as a whole are essentially who we are. In many cases, this is different from what we think consciously.

These insights into qualia and emergence help solve the old issue of how soma and psyche can influence each other. They are two aspects of a single entity. In view of this, Descartes' phrase "*I think, therefore I am"* may be best rephrased as *"I think IS I am"*.

5.2 A Computer Analogy

In a modern computer, there is only one processing thread per CPU. Instructions are executed sequentially, and involve binary operations. Furthermore, each piece of data is stored and processed in one place at any given time. In contrast with this, the human brain is a highly 'parallel and distributed device'. (Rumelhart & McClelland, 1986):

- It is **parallel** because many neurons, and in principle all of them, can be active at the same time. If we then treat the *patterns* of synapses as parallel processing units, the true scope and power of the brain becomes evident.
- It is **distributed** because each 'concept' in our mind is not stored in a distinct locker, kept separate from other concepts. Instead, a large number of processing units work together to allow us to think about a single concept. In other words, the concept is distributed over those processing units. At this 'physiological' level, concepts are therefore intimately intertwined, with each concept sharing processing units with many other concepts. This makes the

human brain/mind extremely powerful when carrying out tasks such as pattern recognition, spontaneous generalization, graceful degradation and automatic content addressability (see article "*Cloud or Clock"*).

Treating the entire brain as a single enormous computer, thoughts can be viewed as the results of processing that occurs in this hardware. In this model, there are three distinct levels as shown below:

hardware level (cells) → processing level → thought level

However, another difference between the brain and a computer invalidates this three-level model:

- In a computer, software processing occurs without any chemical or microscopic physical changes to the hardware. Electrons flow back and forth, but this does not result in any significant hardware changes. When a '1' changes to a '0' and then back to '1', that new '1' is for all intents and purposes identical to the original. If we call this type of change process the computer's *mind*, then the computer has a *mind-body dichotomy.*
- With a human, the processing that takes place at the 'software level' is fundamentally different. Chemical, micro-anatomical, and (in the long term) anatomical changes are associated with the process of thinking. In this sense, the brain changes with each thought. Therefore, we can never think exactly the same thought twice. We have *mind-body unity*.

In summary, in a computer, run-time activity *is the result* of processing that occurs in the hardware. In contrast, human thinking *is* the processing itself. Viewed broadly, every human thought is a hardware change. While most changes in association patterns do not emerge into conscious thought, they do change the same hardware that performs conscious thinking.

5.3 A Brief History of Connectionism

Since the 1940s and 1950s, there has been significant cross-fertilization between neuroscience and computation in the area of activation of networks. For example, a 1943 paper by McCulloch and Pitts dealt with 'formal neurons' as binary units. Then, Donald Hebb suggested in 1949 that when two neurons in the brain became active at the same time, the strength of the connection might be increased, a principle that

has been modeled widely in ANNs. Frank Rosenblatt then proposed his 'Perception Convergence Theorem' in the 1950s, which stated that “If a set of weights existed that would produce the correct responses to a set of patterns, then through a finite number of repetitions of this training procedure the network would in fact learn to respond correctly.” While some of this research was explicitly targeted at modeling the brain, for Rosenblatt and others the primary goal was to create a more general understanding of cognitive performance.

In the 1970s, cognitive science created a 'cognitive revolution' in psychology, providing a successful successor to behaviorism as well as a Chomskian revolution in linguistics. Using symbolic models, there was also a limited amount of research into the subconceptual domain.

By the 1980s, 'classic' cognitive science had become more diverse, but it still adhered to the core principles of the symbolic AI approach. However, cognitive psychology and AI researchers also started to use neural networks as a way of modeling human cognition. The intersection between these two areas in the early 1980s produce the distinctive approach to cognition known as connectionism. Its primary goal was to develop a more complete description of cognition than could be obtained from the rules and symbolic representations of an information processing framework. Both neural plausibility and computational power were attractive to connectionists, primarily because they provided a powerful mechanism for modeling and understanding cognition.

In 1986, Rummelhart and McClelland published '*Parallel Distributed Processing*' which became the 'bible' for PDP, and this was followed in 1991 by 'Connectionism and the Mind', written by W. Bechtel and A. Abrahamsen. Both of these are still classics of research into connectionism, ANN and PDP.

More recently, research work has combined aspects of the symbolic and connectionist approaches. This has helped lay the groundwork for a more pluralistic approach to cognitive science in the 21st century.

5.4 The Allure of the Connectionist Approach

> SEE ALSO ARTICLE: "CLOUD OR CLOCK: IMPLICATIONS OF THE SUBCONSCIOUS ON PLACEBO, DOUBLE-BLIND STUDIES AND MEDICINE IN GENERAL"

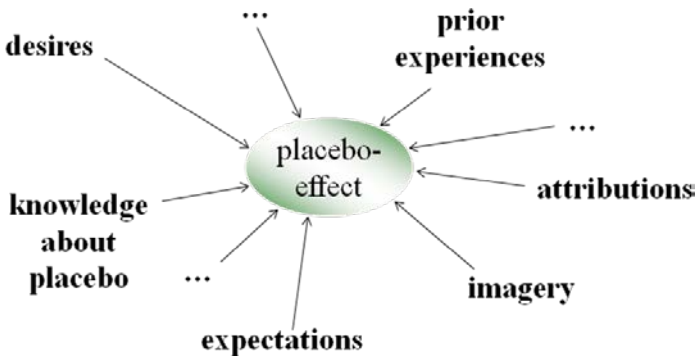
Many properties of networks make them attractive for cognitive modeling, and this has rekindled interest in their use. Some of these properties are described in the sections that follow.

5.4.1 Neural Plausibility

Connectionist networks capture aspects of the coarse architecture of the human brain. However, they do not map clearly to the nervous system in some areas, such as learning through back-propagation procedures.

5.4.2 Satisfaction of Soft Constraints

There are degrees of softness in constraints. 'Rule-based' systems typically occupy the hard end of the spectrum, while neural networks occupy the soft end. However, while neural networks offer a natural way of modeling soft constraints, this association should not be viewed as either exclusive or inevitable. For example, some rule-based systems allow rules to compete probabilistically, provided that they satisfy their antecedents. Conversely, it is possible to design neural networks, such as XOR networks, that provide relatively hard constraints.



Soft constraints on placebo effect

As is shown in the accompanying figure, any concrete instance of the placebo effect satisfies a set of soft constraints that are specific to the particular situation in which the effect occurs. Even when the same person uses the same placebo, the soft

constraints can vary in different situations. For example, a study by Amanzio & Benedetti showed that the brain responded differently to an analgesic placebo depending on whether or not the subject had previously received morphine or another analgesic. (Amanzio & Benedetti, 2006).

5.4.3 Graceful Degradation

When the brain's limits are exceeded, generally it does not crash. Instead, its performance becomes increasingly suboptimal. Confronted with a task that makes too many demands on it, the brain begins to ignore some of these demands and associated information. In other words, the more the brain is overloaded, the less well it functions.

In general, the brain is also quite resilient to damage. Nerve cells die every day, but this does not typically cause impairment of brain function. Even the loss of a large number of nerve cells does not necessarily lead to complete dysfunction, with a gradual nonspecific impairment being the most common outcome. For example, we do not forget how to multiply 12 x 2 while remembering the rest of our multiplication tables – instead, our numeric calculation abilities gradually become more limited.

Traditional symbolic systems do not exhibit this kind of graceful degradation. However, when a number of nodes are removed from an ANN, the system continues to function – albeit in a slightly distorted manner. For example, if an input is normally distributed over eight nodes, the system will still respond normally to most input patterns if one of these nodes is disabled. As damage increases further, the system will make an increasing number of errors, but even these will not be random. The ANN is exhibiting graceful degradation.

5.4.4 Content-Addressable Memory

The brain is able to retrieve the same piece of information using a variety of different cues that are found in the contents of the memory itself. Designing this type of memory access into a symbolic system is challenging, and requires working around the system architecture rather than taking advantage of it. In contrast, connectionist networks perform recall by using the same methods that are used to make

inferences – the system fills in missing pieces of information. When reconstructing a previous state, the system performs the same processing that it does when it constructs a totally new state (confabulation).

5.4.5 Capacity to Learn from Experience and Generalize

An ANN allows prototypes to be extracted, a capacity that is also exhibited by the human brain. In this process, the most widely shared properties become the most active, in part due to the creation of positive feedback loops which further strengthen and refine the prototype.

5.5 Criticism of Connectionism

Jerry Fodor and Zenon Pylyshyn put forward what is perhaps the best-known criticism of connectionism (Bechtel & Abrahamsen, 2002), arguing that connectionist models whose representations fail to exhibit syntactic structure cannot account for major aspects of cognition. They maintained that the analysis of symbolic, non-connectionist processing is the only type of analysis that is relevant to cognitive theory. In their view, connectionism is merely an account of the medium in which symbolic representational processing is implemented, and therefore it is not a basis for theorizing about cognition itself.

They grounded their criticism in the notion that there are different levels of analysis in nature. Within each of these levels – such as molecules, stones and galaxies – we can talk about interactions and causality, but "the story that scientists tell about the causal structure that the world has at any one of these levels may be quite different from the story that they tell about its causal structure at the next level up or down." Furthermore, Fodor has argued elsewhere (Fodor, 1983) that any given function can be implemented using any one of a number of lower-level mechanisms, and that a single lower-level mechanism may be involved in multiple higher-level functions. Fodor and Pylyshyn pointed out that nothing prohibits symbolic operations from being implemented using a parallel architecture, allowing them to be performed much more rapidly than in a classical von Neumann computer.

At the heart of this critism lies the question of whether a 'cloud' or 'clock' model is most appropriate for analyzing the human mind. This issue has been dealt with in the article *Cloud or Clock* which forms part of this thesis.

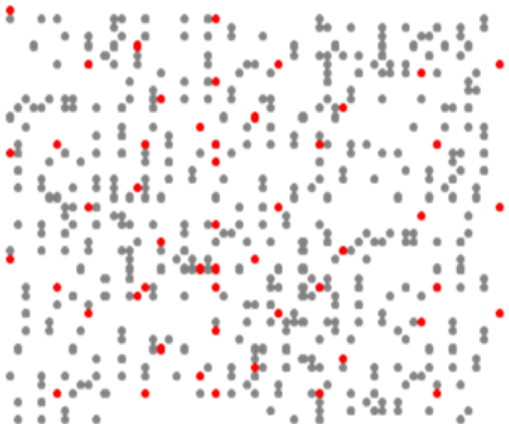
5.6 Associationism in Subconceptual Processing

At the neuronal level, extensive investigation has shown that 'grandmother cells' do not exist. In other words, a concept such as 'grandmother' is not represented by a single cell. This raises the question of how concepts (and subconceptual elements) are stored and processed in the mind/brain.

Instead of there being a one-to-one correspondence between cells and concepts, it appears that a concept is active in the mind when a number of cells are active at the same time. These cells form a relatively small 'network' or 'pattern' which *as a whole* represents the concept.

We can hypothesize that as these patterns become larger and more broadly distributed within the brain, they become more difficult to bring into the realm of consciousness, since the act of activating and maintaining the pattern becomes increasingly complex. Additionally, as patterns become broader, they may have more subconscious influence on both the mind and the body.

While broad patterns are more difficult to activate, they may also be more stable and therefore may have a stronger influence especially in the long term, a characteristic that is also seen in ANNs. Therefore, such broad patterns may determine long-lasting characteristics such as personality and long-term influences of the mind on the body. However, since these patterns are difficult to bring to the conscious level, they are more difficult to study scientifically.



Darker dots form a pattern

In the 17th century, empiricists were primarily concerned with epistemology, believing the knowledge must be grounded in sensory experience. However, their frame of reference also included an account of psychological processes that came to be known as *associationism*. In this account, sensory experiences gave rise to simple ideas – such as *red* and *round* – which in turn were combined into more complex ideas such as *apple*.

Anderson and Bower (Anderson & Bower, 1973) suggest that associationism has four defining features: that mental elements can become associated through experience, that complex ideas can be reduced to sets of simple ideas, that simple ideas are sensations, and that simple additive rules are sufficient to allow the properties of complex ideas to be predicted from their constituent simple ideas. Connectionism can be regarded as a further evolution of associationism, adopting the idea that spatial and temporal proximity breeds connections, and then applying new elements that include distributed representation (coarse coding in particular), hidden units that encode micro-features and enable complex computations on inputs, and nonlinear activation rules. Connectionism also adds mathematical models that describe the dynamics of associative learning, supervised learning, back-propagation, and simulated annealing within self-organizing dynamic networks.

By doing this, connectionism shows that *pattern recognition* is a basic feature of neural networks – these networks are actually devices for mapping one class of patterns to another. They do this by encoding statistical regularities in weighted

connections, which can then be modified in response to experience. This has led to the claim that connectionist networks are highly suitable constructs for modeling human cognition.

In a connectionist view of the human brain, pattern recognition plays a fundamental role at all processing levels, from basic sensation through to high-level reasoning. P. Smolensky suggested that the task of perception could be abstracted by generalizing pattern recognition to account for higher-level cognitive capabilities, stating that "This abstraction includes many cognitive tasks that are customarily regarded as much 'higher level' than perception (e.g. intuiting answers to physics problems) … The abstract task captures a common part of the tasks of passing from an intensity pattern to a set of objects in three-dimensional space, from a sound pattern to a sequence of words, from a sequence of words to a semantic description, from a set of patient symptoms to a set of disease states, from a set of givens in a physics problem to a set of unknowns. Each of these processes is viewed as completing an internal representation of a static state of an external world. By suitably abstracting the task of interpreting a static sensory input, we can arrive at a theory of interpretation of static input generally … that applies to many cognitive phenomena in the gulf between perception and logical reasoning." (Rumelhart & McClelland, 1986, pp. 197-198)

In general, the cerebral cortex does indeed excel at the creation of detailed maps. Some subcortical structures – including geniculate bodies, colliculi, the nucleus tractus solitarius, and the parabrachial nucleus – also create coarse subconceptual maps. Furthermore, "The brain can do more than merely map states that are actually occurring, with more or less fidelity: it can also *transform* body states and, most dramatically, *simulate* body states that have not yet occurred." (Damasio, 2010, p. 93) and "The brain's ravenous map-making addiction leads it to map its own workings – once again, talk to itself. The brain's maps of its own doings are probably the main source of abstract images that describe, for example, spatial placements and movements of objects, relationships of objects, velocity and spatial course of objects in motion, and patterns of occurrence of objects in time and space." (Damasio, 2010, p. 187)

It is entirely reasonable to believe that this ability to make maps can influence physical health and healing, helping us to remain in balance. In nature, organisms both counteract and anticipate imbalances, and our own intelligence may be a part of the same drive. However, when an organism enters a vicious cycle of increasing

imbalances, this drive may also play a role, pushing the organism towards illness rather than health. Unfortunately, this appears to be the case in physical and psychological/psycho-somatic health and illness. It may also lead to addictive behaviors, where the very thing that seems to heighten balance at the conscious level is actually creating imbalance subconceptually. For instance, while a smoker may feel that smoking a cigarette relaxes them, shortly after they may experience increased nervousness.

In our quest to understand psycho-somatics, the subconceptual level has been largely disregarded to date. Instead, the focus has been primarily at the biochemical level. Obviously, there are economic drivers for this, but the intractability of the subconceptual may also play a part. However, gaining an even partial understanding of the role of the subconceptual may be of significant value, since it has the potential to show the importance of 'deeper meaning' in domains such as placebo and empathy, allowing us to assess the pros and cons of various approaches to these areas. In addition, a purely conceptual view is insufficient to develop a complete understanding of depression and psycho-somatic phenomena. Ignoring the intervening subconceptual layer leads to a direct connection between biochemistry and the conceptual, and yet neither of these have 'deeper meaning'. Increasingly, however, research is showing that such 'deeper meaning' has an enormous impact on mental and physical health. This 'deeper meaning' must reside somewhere, and despite both major efforts and popular belief, no biochemical explanation of this has stood the test of time. Antidepressants are a good example of how following such a biochemical hypothesis can lead us astray (cf. Kirsch, 2009). Subconceptual processing offers an alternative explanation to non-conceptual causation of mental and psycho-somatic disorders.

5.7 The Flourishing Domain of Cognitive Neuroscience

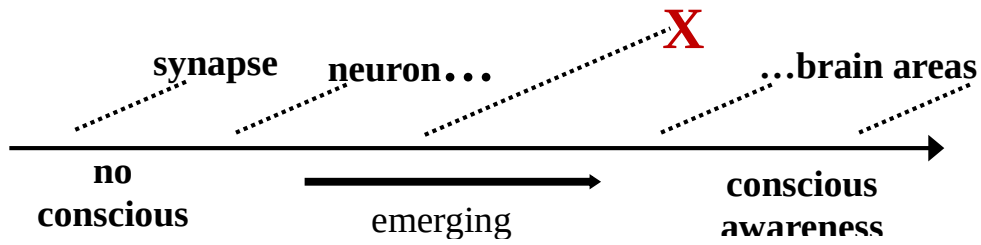
The following passage is taken from Patricia Churchland in 'Brain-Wise': (Churchland, 2002)

> *"The mind that we are assured can dominate over matter is in fact certain brain patterns interacting with and interpreted by other brain patterns…*

Consciousness is, almost certainly, a coordinated pattern of neuronal activity serving various biological functions. This does not mean that consciousness is not real. Rather, it means that its reality is rooted in its neurobiology…

During the last three decades, the pace of discovery in neuroscience has been breathtaking. At every level, from neurochemicals to cells, and onwards to the circuit and system levels, brain research has produced results bearing on the nature of the mind. Coevolving with neuroscience, cognitive science has probed the scope of large-scale functions such as attention, memory, perception, and reasoning both in the adult and in the developing infant. Additionally, computational ideas for linking large-scale cognitive phenomena with small-scale neural phenomena have opened the door to an integration of neuroscience, cognitive science, and philosophy in a comprehensive theoretical framework…

Significant technical progress has been made in recording simultaneously from more than one neuron, and the advent of powerful computers has made the problems of data analysis somewhat more tractable. Nevertheless, the search is on for technical breakthroughs that will really mesh microlevel experimentation with systems-level data. We are also uncertain how to identify what, among the billions of neurons, constitutes one particular network, especially since any given neuron undoubtedly has connections to many networks, and networks are likely to be distributed in space. To make matters yet more interesting, what constitutes a network may change over time, through development, and even on very short time scales, such as seconds, as a function of task demands."



Levels of processing inside brain and mind

The medicine we know today is rooted in ideas taken from physics as it existed around 200 years ago. This was a Newtonian age, and Newtonian physics has now been supplanted by quantum physics. This does not mean that medicine should

evolve into some type of 'quantum medicine', but it *does* indicate that medicine needs to look for a new paradigm, especially in the domain of psycho-somatics. An appropriate candidate for this would seem to be the very stratum from which the human mind emerges. Subconceptual processing is a good alternative to 'Newtonian' medicine in this respect.

5.8 Mind as the Result of the Interplay between Many Brain Regions

All of the regions of the brain that are involved in mind-making have highly differentiated patterns of interconnectivity, which is suggestive of very complex signal integration. "*Ensembles of neurons that are working together to signify some combination of features must synchronize their firing rates. This is probably achieved by oscillations of neuronal activity … What we experience as mental states corresponds not just to activity in a discrete brain area but rather to the result of massive recursive signaling involving multiple regions. And yet … there is some anatomical specificity behind the making of mind, some fine functional differentiation within the maelstrom of global neuron complexity.*" (Damasio, 2010, p. 87) Of course, it is not just regions of the brain that are intermingled when it comes to generating health and illness. Examples of this are as follows:

- An emotion involves the activity of a number of specific brain regions together with several regions of the body. At the same time, given that the brain is highly parallel in nature, we can deduce that many emotions may exert a simultaneous influence. This is borne out in reality. While one powerful emotion may dominate at specific times, at other times several different emotions, as well as other mental 'content', may have a parallel and distributed influence. Since our conscious mind can only deal with so many elements at any given time, we may be unaware of many of these influences. This leads us to overlook our own complexity, so that when specific research, such as that into the 'Stroop effect', shows that these influences are nonetheless present, it comes as a surprise. This is also evident in 'decision making', where many interacting factors push, pull, compete and constrain the final decision that the brain/mind makes. Many of these factors never make themselves known at the conscious level.
- In the brain, processing of visual information is distributed across more than 30 cortical areas. These areas are functionally specialized and hierarchically

organized, and are interconnected by feedforward and feedbackward connections, forming partially segregated modules and pathways for processing different visual stimuli attributes. Extensive evidence has shown that visual experiences can modify pre-existing visual system functionality and connectivity throughout our lives.

- The immune system and central nervous system are much more intimately intertwined than was thought only a few decades ago. Immune cells have such a profound influence on neurons and neuronal networks that they actually participate in the thinking process itself, with immune cells forming part of neuronal networks. Therefore, it is no surprise that the mind/brain has an enormous influence on immune function. Indeed, we can see this effect in the progression of AIDS, multiple sclerosis, rheumatoid arthritis and other diseases. In the case of cancer, we see the clear influence on killer cells. This is not 'magic', but merely discoveries that have arisen out of rapid progress in the field of psychoneuroimmunology. Insights into subconceptual processing may further accelerate developments in this field.

Not all regions of the brain contain hardware that is equally accessible to conceptual processing and overt, conscious awareness. A number of regions are clearly more dispositional. Subcortical "*nuclei are filled with 'dispositional know-how, the sort of knowledge that does not require detailed mapped representations.*" (Damasio, 2010, p. 90) Furthermore, "*The brain did not discard its true and tried device of dispositions in favor of new invention (maps and their images). Nature kept both systems in operation and with a vengeance: it brought them together and made them work in synergy. As a result of the combination, the brain simply got richer, and that is the kind of brain we humans receive at birth … Networks of dispositions run our basic mechanisms of life management (endocrine system, mechanisms of reward and punishment, triggering and execution of emotions…). The basic mechanisms of life influence the operations of the mapping regions in the cerebral cortex.*" (Damasio, 2010, p. 135) "*Dispositions also assist with the processing of a currently perceived image, for instance, by influencing the degree of attention accorded to the current image. We are never aware of the knowledge necessary to perform any of these tasks, nor are we ever aware of the intermediate steps that are taken.*" (Damasio, 2010, p. 144)

We now know that a massive amount of information flows from all parts of the body to the brain. The immense capacity of the brain maps virtually everything, down to

the level of miniscule vasodilations, muscle contractions and inflammations. All of this information travels to the brain, which in turn influences the body in a myriad of ways through feedback loops. Only a tiny proportion of this information actually reaches our conscious mind, with most of it being processed subconceptually. In other words, the information isn't crystallized into concepts. "*The brain knows what the past state of the body (contraction or dilation of smooth muscles, amount of O2 and CO2 concentrated locally in any region of the body, temperature and pH at various locations…) has been and can be told of modifications occurring in that state.*" (Damasio, 2010, p. 94) "*The body is the brain. Under normal circumstances they are hitched to each other from birth to death. Just as important, the mapped images of the body have a way of permanently influencing the very body they originate in. The situation is unique.*" (Damasio, 2010, p. 89) Thus it can be seen that the influences between the brain and the body are extraordinarily large.

The path to consciousness in our brain is permeated by bidirectional influences throughout its entire structure. There has been considerable clarification of these influences in recent decades. For example, 'lowly orders' like thalamus, hypothalamus and upper brainstem form bidirectional stations communicating with virtually every bodily organ at one side and with cortical regions at the other side. This way bodily influences also reach cortical levels as such, meaning that they co-generate and influence what happens there: decision making, reasoning, creativity… We may think that our 'highest mental functions' are independent of 'lowly bodily input' but that is not the case. Nature has not built the neocortex as a single apparatus of rationality, but instead as an additional instrument along with those in the subcortical regions. "*At neither modest nor robust levels do self and consciousness happen in one area or region or center of the brain. Conscious minds result from the smoothly articulated operation of several, often many, brain sites … much as the performance of a symphonic piece does not come from the work of a single musician or even from a whole section of an orchestra … a conductor is now leading the orchestra, but the performance has created the conductor – the self – not the other way around … What each musician contributes does count. But only the ensemble produces the result we seek to explain.*" (Damasio, 2010, p. 23)

It may be appropriate to use the term 'holistic' here. If science continues to confine 'high-level' mental functions to an ivory tower, sooner or later a wave of countervailing sentiment may sweep in the opposite direction in an attempt to

restore the balance. It is an interesting question whether this can explain the surging popularity of CAM in what is supposed to be an age of reason.

Another intriguing question is why the brain segregates the processing of information when it is all derived from a common source and appears unified when we experience a phenomenon. Rueckl et al. showed that a dual task – two tasks or subtasks simultaneously – was more readily learned by an ANN if it had modular components. (Rueckl, Cave, & Kosslyn, 1989) If there is a computational advantage to segregate processing in a connectionist network, at least during the initial learning phase and potentially later on, the same may be true of the brain. Jacobs at al. suggested there may be additional advantages to modular design, including more appropriate generalization (since each expert subnetwork is only responsible for generalization within the scope of its own task), development of more intelligible and useful representations (since the representations are task-specific), and more efficient use of computational hardware (since each expert subnetwork only has to represent a limited number of dimensions). (Jacobs, Jordan, & Barto, 1991)

Returning to emotions, a feeling by definition is the conscious awareness of emotional processing. This processing proceeds subconsciously from the start and involves influences from the body as well as from a dispersion of brain regions and significant feedback. An emotion is reconstituted time and time again within a pattern of influences at the subconceptual level. This also explains why chronic anger can heighten feelings of pain, even when the person is not consciously aware of this 'anger'. Of course, one can object that in such a case, there is no 'anger'. However, that is a semantic question that is less important than whether there is 'something' that can emerge as a conscious feeling, but can still influence the body or create an awareness of acute or chronic pain even if it does not crystallize into a conscious concept. In view of research into the influences of emotion on pain, we have to conclude that this 'something' exists. This is probably also the case with other bodily functions.

5.9 Subconceptual Processing and Philosophy of Mind

If I move my arm, how does that movement come about? If my fear changes my heart rate, how does that happen? Does my fear change my brain, or does my brain

cause me to feel fear? How can the mind influence the body and vice versa, if they are two separate entities, the one material and the other not?

Without taking recourse to metaphysics, this problem becomes insoluble if the mind is defined as a 'non-material' substance. By this definition, the mind cannot influence matter. However, if we explain the mind in more physical terms, it becomes increasingly difficult to maintain the divide between mind and brain. Subconceptual processing brings a new level of understanding to this necessary unification. One wonders what Descartes would have thought if he had the same knowledge that we do today about both the brain and the power of computing.

Descartes also believed that our own perception of the current state of our mind could not be false, and that the contents of our mind were transparent to us. Subconceptual processing shows that these beliefs were equally wrong.

There are several other theories that address the mind/body problem. (Heil, 2004) However, on closer inspection the definitions used in most of these are based upon convention, rather than reflecting things as they are. Here are some examples:

- Substance dualism – E.J. Lowe distinguishes the self from the body in the same way that a boat is distinguished from the collection of planks from which it is made. 'Boat' is therefore a noun that represents this complex collection. Looking at the fine details of the boat, however, ultimately reveals that defining the whole as a boat adds nothing – other than a convenient way to communicate about it. This may be fruitful in its own right, but the point is that it doesn't add anything to reality. There is no ‘boat’ apart from the collection of planks.
- Property dualism – Spinoza regarded thought and extension – being matter taking up space – as fundamentally different attributes or facets of a single substance that thinks and is extended. In fact, SP shows that 'thinking' and 'being extended' overlap to such an extent that they are actually two ways of describing the same thing.
- Parallelism – minds appear to interact with the material world, but the appearance is just that – an appearance. Sequences of mental events and sequences of material events are running in parallel, but this is only co-variation, not causation. Subconceptual processing is compatible with this, only it takes the idea of material events seemingly ‘running in parallel’ to a much deeper level. If the 'mind' runs in parallel with the material world even

in the smallest details, then the question is why the concept is needed at all. If it doesn't run in parallel, then parallelism is wrong, and if it does then parallelism is an unneeded additional layer of explanation.

- Epiphenomenalism – if we grant that the material world is causally closed, it is still possible for material events to have mental byproducts. Mental events can thus result from material causes, but cannot in turn have material effects. In this theory, mental events are 'epiphenomena'. SP, however, shows that mental epiphenomena are not needed to explain cognition. Here, once again, the definition of mental events as 'epiphenomena' is only a definition by convention. There are only different views upon the same thing.
- Functionalism – although immaterial substances – spirits, for example – are conceivable, all computational processes take place in material systems and can be abstracted from them. Of course, one can speak of abstraction without accepting the existence of abstract entities in addition to the concrete entities of time and space. Subconceptual processing shows that in the human brain, any particular realization is bound to a particular material construct. 'Mind' is not independent of 'matter' in the human brain. Additionally, subconceptual processing shows that one cannot simply abstract the mind without risking losing its essence.
- Intentionalism – in explaining a robin's behavior in a garden by referencing beliefs and desires, one adopts what D.C. Dennett calls the 'intentional stance', where we try to *make sense of* and predict the behavior of any creature. (Dennett, 1992) SP adds to this an additional layer of sense in that we can see the robin's behavior as being embedded in its own neuronal patterns that may or may not coincide with ours.
- Identity theory – this deals with identifying mental states with brain states. Subconceptual processing provides more insight into *how* this is realized within the brain.

Finally, the battle in the philosophy of the mind between monism and dualism is at its heart a conflict between reductionism and non-reductionism. Non-reductionists refuse to accept that human beings are *simply* matter. They see the mind as being irreducible, and therefore it must be fundamentally different from matter. This leads directly to dualism. On the other hand, materialists believe that there is only matter,

and therefore the mind arises as a 'property' of this. It appears that many non-reductionists do not want to abandon the idea of 'deeper meaning', and so need to invoke a special 'non-material' substance.

However, seen within a SP framework, the brain is intractably complex and overlaps/coincides with the mind, containing a wealth of 'deeper meaning'. Every change in the mind is a change within the almost infinite space of the brain's processing network. The complexity of the space also makes the question of whether there is something else at the end of this infinity meaningless. At the same time, SP lies much closer to the body than to the idea of a purely conceptual mind.

In SP, there is no reductionism leading to materialism. There is only one thing, and whether one calls it 'matter' or something else, that does not change it. Nevertheless, one can still have different types of meaningful relationships towards this one thing. Different philosophies of mind are about these relationships.

5.10 Subconceptual Processing and 'Causality'

> SEE ALSO ARTICLE: "CAUSAL THINKING IN PSYCHO-SOMATICS, WITH PEPTIC ULCER AS CASE"

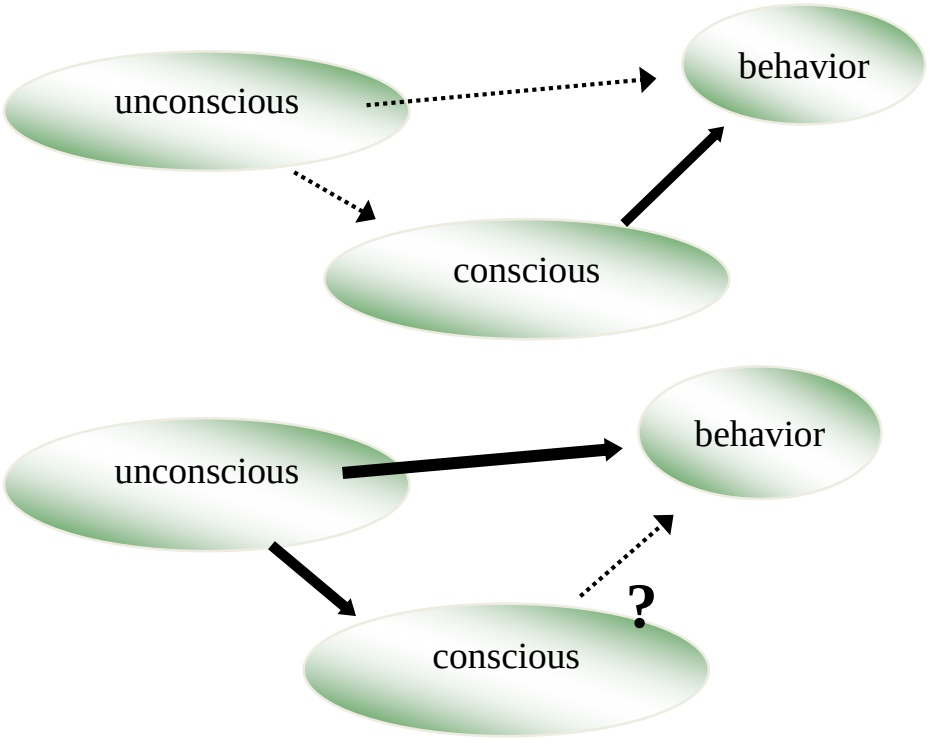
Causal thinking in medicine, and especially in psycho-somatics, is in a dire state. There is an inappropriate search for *the* cause of any concrete illness. Finding *the* cause of a disease gives us a sense of control, relieves tension and eliminates the danger of 'guilt'. In this way, looking for causality serves a function that lies outside causality itself in many cases.

The true complexity of medical causality is far more extensive than just finding *the* cause (cf. Causal Thinking in Psychosomatics). Something can easily be pinpointed as *the* cause, when in reality there are always a multitude of causes. Furthermore, if *the* cause is consistently 'found' to be non-subconceptual, then SP is totally eliminated from the picture. If causality only applies to concepts, then the entire domain of SP risks falling into the gaps of conceptual causality, especially if this belief is applied throughout the entire causal thinking process. In fact, this is happening at present. PUD is an example, as discussed in detail in H. psychologicus (cf. infra). Similarly, our drive to search for causes outside of our own mind/brain makes us

focus on factors such as viruses, enzymes and the environment. A vested interest in not acknowledging the role of SP therefore creates an immense bias that hides under the guise of objectivity.

Theory and experimentation should go hand in hand. Of course, experimental results are valid in their own right, but only by theorizing can we see that much experimentation is relative. In other words, it is only valid within its own circumscribed domain. The presence or absence of confounding factors has a profound influence on results, and eliminating these from experimental designs reduces the extent to which they represent reality.

Correlations do not prove causality. Two entities that appear to be directly causally related may in fact share a mutual cause. SP, although it is often not readily apparent, frequently is this mutual cause. In fact, it has been strongly argued that SP is, in a very profound way, the source that motivates all of our behaviors. The following two figures illustrate how we often think our conscious mind 'causes' our behavior, whereas it is often unconscious processes that give rise to both behavior and conscious processes.



(Un)conscious causality of behavior

SP makes causality more complex in that our behavior can arise from both conscious and subconscious processes. For instance, SP sheds a different light on us not having a strong enough 'will' to overcome a burnout. In fact, a burnout *is* the state where we do not have sufficient motivation to carry on with our normal activities. However, this motivation is not a conscious decision. Therefore, SP may be problematic for many people, since it indicates that there are more things in their mind that can 'cause' illness than they would like to admit. This could lead to guilt heightening the suffering of patients, which should not be taken lightly.

In view of 'causal choice' (selecting a particular cause within a causal space) as an attempt to gain control of the future, this leads to a contradiction when the most interesting ‘cause’ lies in the SP domain. Uniquely in this case, we actually *lose* a degree of control, and therefore it is natural for us to *avoid* turning to SP for an explanation. To do so would go against a basic reason why we engage in causal thinking in the first place. However, from a purely rational point of view, looking to SP makes eminent sense.

5.11 Subconceptual Communication

When a man sees a woman in 'suggestive' clothing, this is meaningful information for him that he may or may not respond to. When he does respond, his reaction is partially or completely non-conscious. In other words, there is a spontaneous change at the subconceptual level. This is becoming more and more apparent as the effect is studied using fMRI – see (Demos, Kelley, Ryan, Davis, & Whalen, 2008) as an example.

In a study by Demos et al., 27 male subjects aged between 28 and 33 were shown images of the faces of 73 women, with the images being 'photoshopped' so that some women’s pictures had large pupils, whereas others had small ones. fMRI showed that there was greater activity in the amygdalae when the pupils were dilated. However, none of the subjects were consciously aware of the differences in pupil diameter.

Therefore, there was a meaningful communication with the male subjects at the subconceptual level, and they responded with a significant change in the brain, while remaining completely unaware of the stimulus at the conscious level. This is an example of what we may term 'subconceptual communication'. Of course, this type of communication occurs continuously – we are subject to unrelenting subconceptual communication, but only a small proportion of this reaches our conscious mind.

As with the example of 'suggestive' clothing, the term 'suggestion' is often used in situations where subconceptual communication occurs. 'Hypnotic suggestion' is a prime example of this, but it is not the only one. At the end of the 19th century, 'suggestion' was increasingly used to indicate this kind of purposeful communication, whether or not it was hypnotic (Sidis & James, 1919).

However, the exact definition of 'suggestion' remains controversial. (Rossi & Rossi, 2007) Milton Erickson thought that 'psychological implication' contributes to suggestion, in that implied thoughts or responses seem to arise spontaneously within subjects in response to external stimuli. The stimulus is not the implication – the implication is created at the subconscious level, evoking and utilizing the subject's own association patterns (Rossi & Rossi, 2007).

Two other definitions of suggestion are as follows:

- McDougall states that suggestion is *"a method of communication, resulting in the acceptance as convictive of the communicated proposition in the absence of logically adequate grounds for its acceptance."* (Put, et al., 2004)
- Eysenck says that suggestion occurs *"when one person attempts to influence another person to believe something, to act in a certain way, or to perceive something along lines that are not congruent with reality. This influence has to be asserted indirectly, i.e. not through bribing or punishment, or attempting to influence him overtly."* (Eysenck, 1991)

Note that all of these definitions exhibit an element of mistrust, with suggestion being seen as bypassing conscious rational or 'critical' thinking. Indeed, the type of suggestion used in classical hypnosis (and in the administration of placebos) has this aim. It needs to be made clear that this is a far cry from the idea of 'suggestion' being used in an open manner. For example, if you tell yourself in a neutral manner to become sexually aroused, then it is likely that nothing will happen. There is no communication with the subconscious. On the other hand, if you imagine an

arousing situation that is in accordance with your specific tastes, then you may become aroused, especially if you are not distracted by your surrounding environment. In the latter case, you are using 'suggestion' on your self in a very open fashion.

Unfortunately, the suggestions that are used in research outside of the field of hypnosis are very simple, often consisting of a few repetitions of phrases such as "You will feel less pain", "This may do you good", or even purely informative phrases such as "This is a new painkiller" (Vase, Riley, & Price, 2002). In reality, suggestion can be far richer, using visualization, metaphors and symbols, deeper implied meaning, and a number of linguistic suggestion techniques. Of course, patients constantly respond to suggestions. *"For example, many surgeons have learned that they receive a much better response from their postoperative patients when they approach them in the morning with the question "How are you feeling?" rather than "How is your pain?" The latter question becomes for some patients a subtle suggestion that to be in tune with their surgeon they must be experiencing pain."* (Spiegel & Spiegel, 2004)

(Auto)suggestion can therefore be defined as any communication to the subconscious, with 'auto' being applied in cases where the person makes the suggestion to themselves, with the person 'speaking' to themselves in a special way. The 'auto' aspect is extremely important, particularly in an ethical sense. In classic hypnosis, the aim is to circumvent the conscious part of the subject's mind, speaking directly to the subconscious and even 'reprogramming' it. However, many hypnosis researchers insist that hypnosis always is, or should be, a type of autohypnosis. If this is the case, then all hypnotic suggestions are also autosuggestions.

(Auto)suggestion can be used in many different ways, either to change the subconscious or to invite it to change by itself. I believe deeply that only the second usage is ethical, and that the first creates a large amount of unneeded but nonetheless warranted resistance to change.

Suggestions may be seen as 'patterns' that are impressed upon someone – as in classical hypnosis or positive thinking – or they can be given as true suggestions as in a 'chef's recommendation'. Dancing may provide an illuminating metaphor towards understanding this. When a couple dance and the man leads, he can either force the lady to follow him or he can invite her to do so. The difference between the two is obvious. It should also be noted that when the lady is forced to follow, there is a danger that she will resist.

In the 'neural network' paradigm, patterns may be forced to change in ways that are not compatible with other patterns. These other patterns may be important in themselves, or may even lie at the heart of what makes the person who they are. This leads to tensions, and 'the lady resists'. Conversely, if patterns are invited to change by themselves, the results are much more valuable and productive.

5.12 Subconceptual Processing and the Subconscious

Subconceptual processing actually works so well that when we engage in introspection, we do not experience our brain but instead our conscious mind. Therefore, it appears as if our mind is independent of our brain – the brain is 'transparent'. Conversely, when we experience things in our body or environment, we generally are not aware of our mind – in this case, it is our mind that is 'transparent'. So, we either experience our mind *or* our body, and so they feel separate. It is precisely *because* SP works so well that we do not perceive the mind and brain as being the same thing.

It is a proven fact that a lot of the activity in the brain doesn't emerge into our consciousness – given our current level of knowledge, no cognitive neuroscientist can deny this. Vision is one area where this has been incontrovertibly proven in many different aspects. An enormous amount of processing occurs from the time light reaches the retina to the point at which we consciously perceive an image. (Zeki, 1993) During this processing, numerous decisions are made simultaneously at many levels. Compared to the unconscious component of visual processing, conscious processing is only a small part.

The same is true of activities in the brain that influence bodily functions through the hypothalamic-pituitary axis (such as hunger, arousal, sleep and autonomic functions), or through direct communication between the central nervous system and immune system. Most of this activity happens without us being consciously aware of it. Furthermore, “covert knowledge is quite sophisticated and should not be regarded as primitive. Its complexity is huge and its seeming intelligence remarkable.” (Damasio, 2010, p. 36)

We can use terms such as 'the subconscious' or 'the unconscious' to denote the subconceptual processing level. However, all of these terms have distracting connotations. In many ways, it is more intuitive to think about the 'deeper', as in

"What are your deepest feelings?", "It touches me deeply.", and "there is much depth in his art and her philosophical thoughts." Our intuition generally points to the deeper layers of the personality, and then gives this 'depth' positive connotations, without creating the impression that this 'depth' is simply something that underlies our consciousness, as in the Freudian 'subconscious'.

Taking the example of saccadic eye movements, it is evident that they are not random, but instead highly purposeful. Each individual eye movement, of which we are not consciously aware, is 'decided upon' in such a way that we grasp the main contents of a scene most efficiently. These highly intelligent decisions are taken at incredibly high speeds, literally in 'the blink of an eye'.

In plainly evolutionary terms, nature engages in massive reuse of its own inventions. High levels of complexity build on lower levels without making them substantially redundant. For instance, the driving force behind our consciousness is located in the brainstem, and yet this remains very similar to those found in animals with much more basic levels of cognitive function. Human 'intrinsic motivation' seemingly does not lie in concepts but instead in subconceptual processes. This subconceptual mind/body basis of intrinsic motivation is also what keeps us alive, by communicating with internal organs, as well as continuously driving our 'modern' brain to perform processing that enhances our ability to survive and procreate. Even in the neocortex, subconceptual processing forms the majority of activities, making massive reuse of this prior 'invention'.

Conceptual thinking was clearly not a predestined objective before it appeared. Instead, the evolutionary drive in the course of time came from advantages engendered by 'down under', and the changes that led to it already gave significant advantages *before* conceptual thinking actually emerged. This goes all the way back to the beginning of evolution. Even "*the lives of cells occur in extraordinary complex universes that formally resemble, in many ways, our elaborate human universe. The world and behavior of a single-cell organism such as the paramecium are a wonder to behold, far closer to who we are than meets the eye.*" (Damasio, 2010, p. 16) Agents such as hormones and neuromodulators were already present in simple organisms. Damasio sees feelings as *"the conscious readout of our body states as modified by emotions… This is also why feelings have been influencing societies and cultures and all their workings … But long before the dawn of consciousness, the configuration of chemical parameters was already influencing individual behaviors in simple creatures … The growth of different kinds of bacteria in a colony is guided*

by such parameters and can even be described in social terms." (Damasio, 2010, p. 56) The progressively more deliberated regulation of the human mind was "*quite a leap, albeit assembled, so far as we can see, on biological continuities.*" Nature evolved the use of subconceptual associations and processing, and has exploited this in ever more complex ways. It drives our consciousness as well as our health.

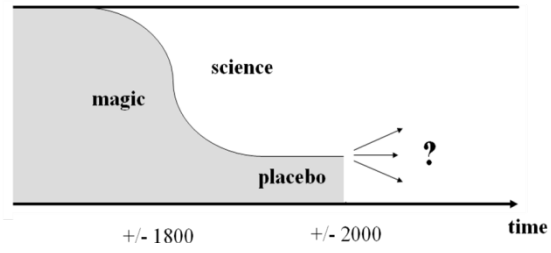
6 Discussion 2: Subconceptual Processing in Medicine

> *"… that I am not merely present in my body as a sailor is present in a ship, but that I am very closely joined and, as it were, intermingled with it, so that I and the body form a unit."* – Descartes (Duncan, 2000)
>
> "*The brain does more than detect and analyze sensory inputs; it creates perceptual experiences even in the absence of external inputs. We do not need a body to feel a body or a physical injury to feel pain.*" (Melzack & Wall, 2008)

6.1 History

In its most narrow sense, 'magical' thinking has been at the core of Western healthcare for millennia. However, while the esoteric powers of shamanic potions are supposed to work outside the familiar constraints of time and space, one can see a confusion between what underlies the placebo effect versus this 'magical' strength from outside. This confusion, along with personal vested interests, is why 'magical' thinking has enjoyed so much commercial success – and continues to do so.

Starting with the ideals of the Enlightenment, there has been an immense effort in healthcare to replace magical thinking with science. This is still an ongoing effort – for example, CAMs still have little or no scientific foundation. Acknowledging the role of the placebo in such alternative therapies is essential. People always look for what 'works', and placebos apparently do – but only by deception. However, the scientific question is *what exactly works* and *towards what end* is it supposed to work. Furthermore, should we care? In asking these questions,



Placebo as remnant of former magic

we are facing a profoundly moral choice that may deepen medical science itself (cf. *Open Placebo*).

Modern medicine is based on the paradigm of waging war on the 'enemy' – a disease – using a therapeutic 'arsenal'. When these weapons do not work, the response is usually to step up the attack. However, viewing psycho-somatics from the subconceptual processing perspective, 'diseases' such as depression, addiction, obesity and many gastrointestinal disorders are not purely due to external influences. Instead, they arise from and exist within the patient. There is no point in patients trying to wage war on themselves. Instead, they need tools to reinforce their 'inner strength' so that symptoms diminish naturally. This change can be likened to the shift from Newtonian physics to quantum physics. Here, the Newtonian paradigm is not being discarded, but instead occupies a place *within* a broader quantum framework.

6.2 Mind-Body Connections: how the Mind can Heal the Body

If you create a realistic mental image of a dangerous monster, your heart will start to pound. This shows that the pathways that lead from the mind/brain to the body can be activated purely by imagination. In this example, both blood pressure and heart rate are influenced by threatening imagery. More broadly, this is also the case with blood perfusion through the skin (emotional blushing) and many other 'autonomic' or 'semi-autonomic' bodily functions. Observe the bodily changes in someone who is watching a scary movie or a romantic one, and this will become apparent. Similar effects occur when they merely recall watching the movie, and so visualization is one type of (auto)suggestion.

Pain is always a sensation, rather than a purely physical phenomenon. When a mother kisses her child's bruised knee to alleviate the pain, this is indeed effective, but is due to the 'deeper meaning' of the kiss, rather than any physical or magical energy flowing from the mother's lips. Therefore, this also is a type of suggestion, putting it beyond doubt that suggestions can have a physical influence.

The body and the mind are not two isolated components within a whole human being. Mind *is* matter in action, and so in a way the title of this section is misleading – the mind heals *itself*. Or, it is just as valid to say that the body *changes itself*.

However, from a heuristic standpoint, it is worthwhile to speak of the mind and body as being separate.

So, to ask the question once again, do the workings of the mind have substantial consequences for long-term health and well-being?

The following table shows various mechanisms through which, according to current research, the mind may influence sickness and health.

Mechanism	**Examples of Conditions**	**Some references to PubMed articles**
Skeletal muscle tension	Lower back pain, wry neck	• Ghaffari M, Alipour A, Farshad AA, Jensen I, Josephson M, Vingard E.Effect of psychosocial factors on low back pain in industrial workers. Occup Med (Lond). 2008 Aug;58(5):341-7. • Holmström EB, Lindell J, Moritz U. Low back and neck/shoulder pain in construction workers: occupational workload and psychosocial risk factors. Part 1: Relationship to low back pain. Spine (Phila Pa 1976). 1992 Jun;17(6):663-71. • Nusbaum F, Redouté J, Le Bars D, Volckmann P, Simon F, Hannoun S, Ribes G, Gaucher J, Laurent B, Sappey-Marinier D. Chronic low-back pain modulation is enhanced by hypnotic analgesic suggestion by recruiting an emotional network: a PET imaging study. Int J Clin Exp Hypn. 2011 Jan;59(1):27-44. • Scheidt CE. [Clinical and psychometric findings in spasmodic torticollis].

		Psychother Psychosom Med Psychol. 1995 May;45(5):183-91. • Gündel H, Wolf A, Xidara V, Busch R, Ladwig KH, Jacobi F, von Rad M, Ceballos-Baumann AO. High psychiatric comorbidity in spasmodic torticollis: a controlled study. J Nerv Ment Dis. 2003 Jul;191(7):465-73.
Smooth muscle tension	Irritable gut syndrome	• Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. J Neurogastroenterol Motil. 2011 Apr;17(2):131-9. • Chang L. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. Gastroenterology. 2011 Mar;140(3):761-5. • Price DD, Zhou Q, Moshiree B, Robinson ME, Verne GN. Peripheral and central contributions to hyperalgesia in irritable bowel syndrome. J Pain. 2006 Aug;7(8):529-35. • Price DD, Craggs JG, Zhou Q, Verne GN, Perlstein WM, Robinson ME. Widespread hyperalgesia in irritable bowel syndrome is dynamically maintained by tonic visceral impulse input and placebo/nocebo factors: evidence from human psychophysics, animal models, and neuroimaging. Neuroimage. 2009 Sep;47(3):995-1001.

Regional blood flow	Raynaud's phenomenon, coronary artery spasms	• Cf. article “The choked heart and how to release it” in this thesis
General blood flow	Hypertension, hypotension	• Mann SJ. The mind/body link in essential hypertension: time for a new paradigm. Altern Ther Health Med. 2000 Mar;6(2):39-45. • Gasperin D, Netuveli G, Dias-da-Costa JS, Pattussi MP. Effect of psychological stress on blood pressure increase: a meta-analysis of cohort studies. Cad Saude Publica. 2009 Apr;25(4):715-26. • Esler M, Eikelis N, Schlaich M, Lambert G, Alvarenga M, Dawood T, Kaye D, Barton D, Pier C, Guo L, Brenchley C, Jennings G, Lambert E. Chronic mental stress is a cause of essential hypertension: presence of biological markers of stress. Clin Exp Pharmacol Physiol. 2008 Apr;35(4):498-502.
Immune system	Eczema, asthma, allergic rhinitis, infection progression including HIV	• Lonne-Rahm SB, Rickberg H, El-Nour H, Merin P, Azmitia EC, Nordlind K. Neuroimmune mechanisms in patients with atopic dermatitis during chronic stress. J Eur Acad Dermatol Venereol. 2008 Jan;22(1):11-8. • Suárez AL, Feramisco JD, Koo J, Steinhoff M. Psychoneuroimmunology of psychological stress and atopic dermatitis: pathophysiologic and

		therapeutic updates. Acta Derm Venereol. 2012 Jan;92(1):7-15. • Peters EM, Liezmann C, Klapp BF, Kruse J. The neuroimmune connection interferes with tissue regeneration and chronic inflammatory disease in the skin. Ann N Y Acad Sci. 2012 Jul;1262:118-26. • Vig RS, Forsythe P, Vliagoftis H. The role of stress in asthma: insight from studies on the effect of acute and chronic stressors in models of airway inflammation. Ann N Y Acad Sci. 2006 Nov;1088:65-77. • Quarcoo D, Pavlovic S, Joachim RA. Stress and airway reactivity in a murine model of allergic airway inflammation. Neuroimmunomodulation. 2009;16(5):318-24. • Kalogeromitros D, Syrigou EK, Makris M, Kempuraj D, Stavrianeas NG, Vasiadi M, Theoharides TC. Nasal provocation of patients with allergic rhinitis and the hypothalamic-pituitary-adrenal axis. Ann Allergy Asthma Immunol. 2007 Mar;98(3):269-73. • Czubalski K, Zawisza E. The role of psychic factors in patients with allergic rhinitis. Acta Otolaryngol. 1976 May-Jun;81(5-6):484-8. • Bavbek S, Kumbasar H, Tuğcu H, Misirligil Z. Psychological status of patients with seasonal and perennial

		allergic rhinitis. J Investig Allergol Clin Immunol. 2002;12(3):204-10. • Balbin EG, Ironson GH, Solomon GF. Stress and coping: the psychoneuroimmunology of HIV/AIDS. Baillieres Best Pract Res Clin Endocrinol Metab. 1999 Dec;13(4):615-33. • Cruess DG, Leserman J, Petitto JM, Golden RN, Szuba MP, Morrison MF, Evans DL. Psychosocial-immune relationships in HIV disease. Semin Clin Neuropsychiatry. 2001 Oct;6(4):241-51.
Hormones	Menstruation disorders, pain (via endorphins)	• Lachowsky M, Winaver D. [Psychogenic amenorrhea]. Gynecol Obstet Fertil. 2007 Jan;35(1):45-8. • Facchinetti F, Demyttenaere K, Fioroni L, Neri I, Genazzani AR.Psychosomatic disorders related to gynecology. Psychother Psychosom. 1992;58(3-4):137-54. • Cf article “Subconceptual Processing: Nonspecific Factor of Chronic Pain” in this thesis
Inflammatory reactions	Rheumatic arthritis, Crohn's disease	• Malysheva O, Pierer M, Wagner U, Baerwald CG. [Stress and rheumatoid arthritis]. Z Rheumatol. 2010 Aug;69(6):539-43. • Straub RH, Härle P. [Stress, hormones, and neuronal signals in the pathophysiology of rheumatoid arthritis. The negative impact on chronic inflammation]. Med Klin

		(Munich). 2005 Dec 15;100(12):794-803. • Evers AW, Zautra A, Thieme K. Stress and resilience in rheumatic diseases: a review and glimpse into the future. Nat Rev Rheumatol. 2011 Jun 21;7(7):409-15. • Maunder RG, Levenstein S. The role of stress in the development and clinical course of inflammatory bowel disease: epidemiological evidence. Curr Mol Med. 2008 Jun;8(4):247-52. • Marín-Jiménez I. [The placebo effect in inflammatory bowel disease]. Gastroenterol Hepatol. 2009 Oct;32 Suppl 2:44-9.
Nervous system irritability	Heart palpitations, tremors	• Ziegelstein RC. Acute emotional stress and cardiac arrhythmias. JAMA. 2007 Jul 18;298(3):324-9. • Barsky AJ, Delamater BA, Clancy SA, Antman EM, Ahern DK. Somatized psychiatric disorder presenting as palpitations. Arch Intern Med. 1996 May 27;156(10):1102-8. • Barsky AJ, Ahern DK, Bailey ED, Delamater BA. Predictors of persistent palpitations and continued medical utilization. J Fam Pract. 1996 May;42(5):465-72. • Redondo L, Morgado Y, Durán E. [Psychogenic tremor: a positive diagnosis]. Neurologia. 2010 Jan-Feb;25(1):51-7. • Jankovic J, Vuong KD, Thomas M. Psychogenic tremor: long-term

		outcome. CNS Spectr. 2006 Jul;11(7):501-8.
Behavioral changes resulting from deep motivation	Losing weight, quitting smoking	• Carano A, De Berardis D, Gambi F, Salerno MR, Campanella D, Castrovilli M, Cotellessa C, Ferro FM. [Psychopathologic patterns in obesity]. Ann Ital Chir. 2005 Sep-Oct;76(5):461-4. • Dallman MF, Pecoraro N, Akana SF, La Fleur SE, Gomez F, Houshyar H, Bell ME, Bhatnagar S, Laugero KD, Manalo S. Chronic stress and obesity: a new view of "comfort food". Proc Natl Acad Sci U S A. 2003 Sep 30;100(20):11696-701. • Gundersen C, Mahatmya D, Garasky S, Lohman B. Linking psychosocial stressors and childhood obesity. Obes Rev. 2011 May;12(5):e54-63.
Normal mind-body interactions	Relaxation, sleeping more soundly	• Pigeon WR. Diagnosis, prevalence, pathways, consequences & treatment of insomnia. Indian J Med Res. 2010 Feb;131:321-32. • Baglioni C, Spiegelhalder K, Lombardo C, Riemann D. Sleep and emotions: a focus on insomnia. Sleep Med Rev. 2010 Aug;14(4):227-38. • McCall WV, D'Agostino R Jr, Dunn A. A meta-analysis of sleep changes associated with placebo in hypnotic clinical trials. Sleep Med. 2003 Jan;4(1):57-62.

In many of these examples, several mechanisms can act simultaneously. For example, regional blood flow plays an important role in many disorders where other mind-body interactions also have an influence. In addition, mind-body influences may act together with other influences in an overall pattern that, *as a pattern*, can be seen as the 'cause' of the illness. Peptic ulcers are an example of this (see *H .psychologicus*).

However, in many domains it is not known how *large* and *lasting* the mind's influence on the body is. Is the mind powerful enough to bring on – or cure – many so-called psycho-somatic diseases, or maybe even cancer? The truth is that we do not know, but that does not diminish the importance of the question.

Of course, we do know in part. Experiments with mice have repeatedly shown that stress clearly influences the development of certain types of cancer, such as of the prostate (Hassan, et al., 2013) and breast metastasis (Sloan, et al., 2010). So the question becomes not whether it is possible, but whether it is possible *in humans* as opposed to mice. Obviously, answering this question is impossible on ethical grounds – we cannot do the same experiments on humans that we do on mice. Its complexity also makes it infeasible – our mental world is much more complex than that of mice. However, we *can* ask the following perfectly rational question: in view of this complexity, why shouldn't this apply in humans even more than it does in mice?

6.3 Why Is There Relatively Little Proof?

If the mind has significantly more influence over the body than we currently know, then why hasn't this been shown by scientific research to date? There are several explanations for this:

- There is actually a fairly large body of proof, but it is not well known within most fields of medicine.
- There has been little financial investment in this area, and it is obviously of little interest to the pharmaceutical industry.
- Ethical concerns quite rightly impede scientific investigation, as in the example with mice previously discussed.

- The 'deeper meaning' of things is very difficult to investigate using present-day scientific techniques. Science as we know it is not designed for areas such as this, but instead for domains that address clear-cut conceptual entities with 'sufficient and necessary characteristics'. Deeper meaning is very difficult to conceptualize, and therefore it is hard to investigate – people react very differently under similar circumstances. For example, when a parent dies one person may cry, whereas another may look forward with anticipation to the reading of the will. Similarly, someone may have enjoyed professional success, but harbor a deep resentment because of the impact on their social life and personal time.
- The 'real' world in which deeper meaning exerts its influence is very difficult to control. There is always a multitude of confounding factors, making good science very difficult. For instance, double-blind studies in the subconceptual processing domain are almost impossible.

However, while further proof of the mind's influence on the body is needed, there is little or no well-constructed evidence to the contrary. Of course, to take a balanced view, this also may be due to the factors just discussed.

6.4 Subconceptual Processing and Placebo

SEE ALSO ARTICLE: “THE PLACEBO EFFECT – HOW THE SUBCONSCIOUS FITS IN”

SEE ALSO ARTICLE: “FROM PLACEBO TO ‘OPEN-LABEL PLACEBO’ TO OPEN ALTOGETHER”

SEE ALSO ARTICLE: “PLACEBO HAS MANY SIDE-EFFECTS”

SEE ALSO ARTICLE: “CLOUD OR CLOCK: IMPLICATIONS OF THE SUBCONSCIOUS ON PLACEBO, DOUBLE-BLIND STUDIES AND MEDICINE IN GENERAL”

SEE ALSO ARTICLE: “INFLUENCE ON COGNITIVE FUNCTION IN HEALTHY, PARTIALLY SLEEP-DEPRIVED YOUNG ADULTS BY THEIR ASSUMPTIONS ABOUT TREATMENT IN A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL WITH METHYLPHENIDATE”

> "*Suppose the experiential factors that are necessary and sufficient for the placebo effect become established and well-characterized. Knowledge of these factors could then be more directly and optimally utilized by both patients and healthcare providers. The concept of 'placebo manipulations' would shift in emphasis from reliance on outside authority to the patients' active participation in developing optimal psychological conditions for therapeutic effects.*" (Price & Fields, 1997)

> "*The history of the placebo effect teaches us that the tremendous acceleration in the incidence of addiction to prescription drugs and of stress-related illnesses may be as unnecessary as it is undesirable. Clearly, the challenge for the modern healing arts is to develop methods for freeing persons to exercise their self-healing competencies without reducing their sense of self-control and responsibility. From this point of view, it is not good enough that patients in fact have that control and are exercising it; they must also recognize that fact. The potential benefits and ramifications of developing competence-mobilizing procedures that also enhance our sense of competence, autonomy, and self-control are enormous and wide-reaching."* (Plotkin, 1985)

6.4.1 The Definition of Placebo

There is still controversy as to the exact definition of 'placebo'. One that is much cited comes from Shapiro & Shapiro: "*A placebo is any therapy (or that component of any therapy) that is intentionally or knowingly used for its nonspecific, psychological, or psychophysiological, therapeutic effect, or that is used for a presumed specific therapeutic effect on a patient, symptom, or illness but is without specific activity for the condition being treated." A.K. Shapiro, E. Shapiro, 1997* (Shapiro & Shapiro, 1997)

The boundary between placebo and suggestion (as in hypnosis) is vaguer than one would expect. Even a 'pure' placebo pill does not work on its own – the meaning of the concrete placebo must be molded by accompanying suggestion(s). For instance, this can be a belief that the subject already has, as in "Pills work.", or a simple statement by the prescriber, such as "This medication is very good." One can go further and provide suggestions such as "Imagine how this pill will dissolve in your

body and reach the places where it is needed." Suggestions can also be more open, as in "This pill works because you make it work.", or even "You can imagine taking these pills and letting them work for you." In fact, the actual physical placebo may be unnecessary (cf. *From Placebo to Open Placebo*). Overall, this shows how important attitudes are when physicians prescribe medication.

6.4.2 The Placebo Effect Is Real and Powerful

The general consensus is that the placebo effect is both real and powerful. Robust placebo effects have consistently been found in scientific research (Wampold, Imel, & Minami, 2007). In one case, a meta-analysis of clinical trials by Hrobjartsson and Gotzsche compared active treatment to a placebo or no treatment at all, and concluded that the placebo effect is only small (Hrobjartsson & Gotzsche, 2001). However, (Wampold, Minami, Tierney, Baskin, & Bhati, 2005) presented a reanalysis of the same trials, and showed that disorders are in fact influenced by placebos in such a way that where the trial design is adequate to detect these effects, the placebo effect is large and robust – and can even exceed the therapeutic effect of the active treatment by as much as 20% in specific cases (Wampold, Imel, & Minami, 2007). Furthermore, the placebo effect was as strong measured objectively as subjectively.

Specific studies have shown that a placebo can have 56% of the effect that morphine does (Evans, 1985), and can be as effective as a hidden intravenous injection of 8 mg of morphine (Levine & Gordon, 1984). Another study has shown that a placebo cream can result in a mean pain reduction of 46% to 57%, compared to a non-treatment group (Benedetti & Arduino, 1999). Only taking placebo responders into account, the average pain reduction factor resulting solely from the placebo effect has been shown to be between 3.3 (Levine & Gordon, 1984) and 5 (Benedetti, 1996) out of 10 on a visual analog scale, with a reduction of 2 points being clinically significant.

We may think that something that appears powerful, such as a specific CAM, cannot possibly be a placebo. However, what if a placebo *is* that powerful in the most placebogenic circumstances? People have believed for millennia in the health-giving power of many things that, with hindsight, proved to be nothing but placebos

(Shapiro & Shapiro, 1997). This has been known for a long time, as is demonstrated by H. H. Goddard's commentary from 1899:

> "*Cures by mind-cure exist, but are in no respect different from those now officially recognized in medicine as cures by suggestion … We have traced the mental element through primitive medicine and folk medicine of today, patient medicine, and witchcraft. We are convinced that it is impossible to account for the existence of these practices, if they did not cure disease, and that if they cure disease, it must have been the mental element that was effective.*" (James, 1985, p. 96)

Turning to modern evidence, neurophysiology and neuroimaging increasingly show that the placebo effect is real. For example, placebos influence depression through the release of serotonin, affect inflammation through cortisol release (Hashish, Harvey, & Harris, 1986), and influence Parkinson's disease by releasing dopamine (Hunter, 2007). Above all, neuroimaging has shown the importance of the placebo response in neuroscience and biomedicine (Koshi & Short, 2007). For instance, a landmark 2002 PET study by Petrovic et al. found a remarkable overlap in the brain areas that are activated by placebos and by a powerful opioid (remifentanil).

6.4.3 Placebo as Subconceptual Communication

Many possible explanations for the placebo effect have been put forward, such as hope, expectancy, belief and conditioning. We have investigated the majority of these in an extensive literature survey, and have shown how these can be distilled into the phenomenon of 'communication with the subconscious' (cf. *The placebo effect – how the subconscious fits in*). Common to both analgesic placebos and suggestion is the presence of stimuli that do not produce any physiological effect, and yet reduce the perception of pain by producing changes in the brain. In the case of suggestion, the stimuli are verbally communicated to the patient. Placebo stimuli include medications, procedures, devices and similar artifacts (De Pascalis, Chiaradia, & Carotenuto, 2002). In both cases, however, the real stimuli are 'meaningful patterns'. A meaningless placebo does not work, and therefore is not actually a placebo. A placebo only has an effect when it acquires a meaning such as "This will cure me." Even the difference between a placebo and a nocebo lies in the suggestions that accompany them (Benedetti, Lanotte, Lopiano, & Colloca, 2007).

When an inert substance is administered together with an analgesic suggestion, subjects experience an analgesic placebo effect. However, if the same substance is accompanied by a hyperalgesic suggestion, subjects show a hyperalgesic nocebo effect. Benedetti et al. (Benedetti, et al., 2003) demonstrated the same principles when patients were preconditioned with ketorelac, a non-opioid analgesic. Thanks to recent advances in fMRI, PET and SPECT, we can see the effects of this in the brain. Brain imaging shows that verbal suggestions of decreased pain can activate endogenous opioids (Amanzio & Benedetti, 2006), whereas suggestions of increased pain can activate cholecystokinin (CCK) (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006).

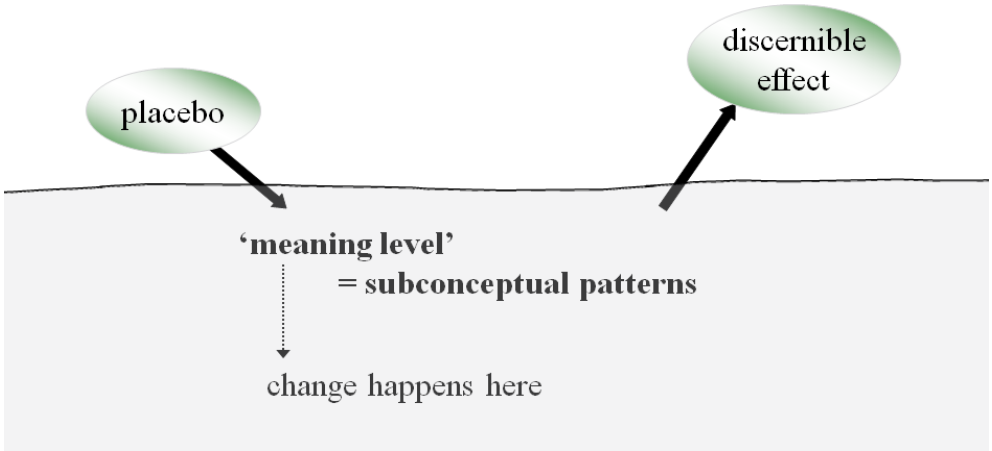
It is also interesting to note that an existing placebo effect can actually be *heightened* by verbal suggestions. For example, in a laboratory study by De Pascalis et al. (De Pascalis, Chiaradia, & Carotenuto, 2002), the largest analgesic placebo effect was experienced by subjects who received analgesic suggestions.

Suggestion is also dependent on context. For instance, when the price of a product is raised, this suggests that it is more valuable. The same applies to placebos. For instance, in one study, a group of subjects was told that an analgesic placebo cost $0.10, whereas another group was told that it cost $2.50. Within the first group, 61% reported pain relief from electrical shocks, whereas 85.4% in the second group did so (Waber, Shiv, Carmon, & Ariely, 2008). These types of 'contextual patterns' may be very broad. A physician's own beliefs may play a part, even if they do not consciously communicate these to their patient. Even more broadly, attitudes and beliefs within the medical community as a whole may have a strong influence.

Several researchers have pointed to expectancy itself as the basis of the placebo effect (Price, et al., 1999) (De Pascalis, Chiaradia, & Carotenuto, 2002). As explained in the earlier discussion of neural networks in this thesis, 'expectancy' can be viewed as subconceptual, making expectancy another type of (auto)suggestion. However, other bases are possible – for example, imagery can be represented by a subconceptual pattern without expectancy being involved.

Anthropological studies show that the response to the 'meaning' of placebos in healing encounters is neither solely nor predominantly conscious in nature (Thompson, Ritenbaugh, & Nichter, 2009). Rather, it results at least partially from 'embodied experience', where the body is viewed *"not as the passive site of medical intervention, but as the penultimate multisensory organ and the locus of lived experience"* (Merleau-Ponty, 1964). Here, the body is the "*site of interface with the*

physical, social and cultural world, and thus our experience in and of the world is perceived, first and foremost, by *and* in *the body."* (Merleau-Ponty, 1964) Our experience of being in the world is primarily 'embodied' and is only secondarily translated into conscious meaning (Thompson, Ritenbaugh, & Nichter, 2009). This anthropological 'embodied experience' is closely paralleled by subconceptual processing.



'Meaning level' between placebo and placebo-effect

As we gain deeper insights into the placebo phenomenon through the study of subconscious processing, this raises the issue that placebos may create many more side effects than is currently thought (cf. *Placebo Has Many Side Effects*).

6.4.4 Placebo and Double-Blind

> SEE ALSO ARTICLE: "SERIAL TREATMENT ASSUMPTION TESTING (STAT) TOWARDS BETTER EVIDENCE FOR EVIDENCE BASED MEDICINE"

In double-blind studies, subjects do not 'know' the group to which they belong. However, what does it mean to 'know' something? For instance, the subject may not 'know', but their body does or the subconscious does. This hypothesis can be investigated by asking both the subject and the physician which group the subject is

in, and then comparing this 'treatment assumption' to reality. When a subject assumes they have received active medication, this may be because the medicine is very effective, because it has side effects, or because of some other knowledge. The literature shows that the assumptions are largely correct when the question is asked after the study is complete:

- 83% of physicians make the right assumption (14 published studies)
- 72% of subjects make the right assumption (17 published studies)
- 63% of others make the right assumption (7 published studies)

With cross-over studies (where active medication and placebos are alternated over several weeks), the percentages are even higher:

- 100% of physicians assume correctly
- 93% of subjects assume correctly
- 75% of others assume correctly

Factors that serve as indicators of which treatment subjects have received include the following:

- The severity and pattern of side effects – for instance, orthostatic hypotension associated with antidepressants
- The strength and pattern of positive therapeutic effects
- When subjects actively try to determine whether they have received a placebo based upon external appearance, flavor or even chemical tests (Shapiro & Shapiro, 1997, p. 204)

The logical consequence of this is that double-blind studies may not be as blind as we generally think (cf. *Serial Treatment Assumption Testing*). This leads to a paradox: the only perfect active placebo is the medication itself. Using the active medication as a placebo would, of course, be nonsensical – and therefore conducting a 100% perfect medical experiment appears impossible.

6.4.5 Placebo and Psychotherapy

In psychotherapy, rigorous scientific double-blind studies are not possible. Therefore, the influence of the placebo effect can never be eliminated from

experiments. This makes rational theorizing more important in psychotherapy than in other domains. It makes no sense to treat the mind as a black box, since then it is not possible to develop rational theories. The alternative – creating theories on the basis that it 'feels it might be like this' – hardly seems a good alternative.

There are good reasons to think that any current theory about psychotherapy is really a pseudo-rationalization of a combination of empathy and the placebo effect. However, when empathy and placebos are placed at the core of psychotherapeutic theory, there is no longer any need for pseudo-rationalization. At this point, we can start to examine psychotherapy in a rational way – and this could lead to a significant paradigm shift.

This also brings to the fore the question of covert and overt use of SP. For example, covert use occurs when a patient is told that a pure placebo has an actual therapeutic effect, while the prescribing physician knows that it does not. Overt use is when both the physician and patient know that the healing power comes from a deeper communication, and that the patient themselves is ultimately the 'cure'.

6.4.6 Consequences for CAM

Alternative medicines and other 'healing methods' suffer from a lack of scientific rigor. However, as well as the effect of the caregiver's empathy, they also create a significant placebo effect in the patient. Patients may feel that this is all they need, but there are negative consequences of this (cf. *Placebo has MANY side-effects*). In the end, 'truth' may be what is most important in health and well-being.

The existence of alternative medicines shows that people long to be taken care of in a way that modern-day science does not provide. Where this longing is not just wishful thinking, there is no reason to reject it from a scientific perspective. With resolve and insight, science can go much further in this area than it does today. However, it needs to be prepared to be critical of *all* sides, and understanding the nature of deeper meaning is central to this.

6.5 Subconceptual Processing and Empathy

SEE ALSO ARTICLE: "EMPATHY BEYOND THE CONCEPTUAL LEVEL – CORE NONSPECIFIC FACTORS OF PSYCHOTHERAPY"

6.5.1 What Is Empathy?

In general, empathy can be seen as the ability to understand another person's feelings, thoughts and motives in depth, both cognitively and affectively (Batson, et al., 1991). However, there are many other definitions and related concepts, such as altruism, sympathy and compassion. What is needed is an agreed, up-to-date set of working definitions that also clearly distinguish empathy from the placebo effect. Brain neuroimaging is increasingly providing data that has strong implications for creating such a clear definition (Goubert, et al., 2005).

For a large part of the 20th century, empathy was seen merely as cognitive labeling of emotional states for the most part. Fortunately, our understanding has evolved in recent decades. Halpern asserted in 2003 that "*the function of empathy is not merely to label emotional states, but to recognize what it feels like to experience something. That is why empathy is needed even when it is quite obvious what emotion label applies to a patient*" (Halpern, 2003, p. 671). In medical practice, if a physician can only coldly label a patient's emotions and thoughts, the patient will not feel deeply understood.

'Altruism' is a fuzzy term that is sometime confounded with empathy. Moreover, there are several ways in which 'selfless' altruism can be viewed as egoism in disguise. For example, so-called altruistic behavior may be directed towards a goal of gaining social or personal reward, such as praise, pride, or the good feeling of behaving altruistically. It can also have the goal of avoiding social or personal punishment, such as guilt or shame (Hein & Singer, 2008). When altruism really is egoism in disguise, it can have negative effects. For example, in an attempt to cope with his own 'altruistic' though actually egocentric distress, a physician may underestimate his patient's pain (Hein & Singer, 2008), and under-treat the patient as a result – or, even worse, avoid contact. On the other hand, the physician may also overestimate the patient's pain by projecting themselves into the patient's position, and then overreact or catastrophize because they have no direct control of the pain that they themselves experience through the patient. The physician then communicates this overestimation to the patient, who as a result of this starts to

experience more pain (Banja, 2006). In this situation, empathy can hurt the empathizer, leading to burn out (Halpern, 2003).

6.5.2 Empathy 'Beyond'

In the context of subconceptual processing and subconceptual communication, the way we understand and even practice empathy gains additional meaning and importance. For example, empathy is about a patient feeling in deep contact with the caregiver, and knowing that the caregiver has a deeply felt understanding of who the patient really is. When communication is purely conceptual, it does not feel empathic and may even increase the sense of loneliness and suffering that accompanies chronic functional pain, depression and other conditions. Real empathy seems to lie beyond the conceptual level (cf. *Empathy Beyond the Conceptual Level*).

This may also shed light on the all-important role of nonspecific factors in psychotherapy, which many researchers assert are its only active principle (Ahn & Wampold, 2001) (Wampold, 2001; Kirsch, 2005; Mathiasen, 2006). Empathy and placebo *are* these nonspecific factors, and are also most probably the active ingredients in the apparent successes of complementary and alternative medicine. Of course, they also play a significant role in regular medicine. In particular, empathy allows physicians to obtain much more information from their patients, saving a lot of time and effort. For example, physicians can be empathic in the way that they perform their examinations, and it is important to note that this does not have to be time-consuming.

Empathy 'beyond' brings a feeling of closeness, but one may wonder why this is the case. Concepts are always distant approximations of the 'patterns' that exist inside the mind at the subconceptual level. This is why science finds it so difficult to conceptualize and operationalize the 'deeper' aspects of our mind into useful elements of experimental science. This is also why purely conceptual science feels 'cold' when human beings are involved. Indeed, purely conceptual communication itself feels 'cold'. People only start to feel close when they are able to transcend the conceptual level. It is only then that we can start to 'see' another person and be open with them, creating a very different and always personal relationship.

Because of this, the subconceptual processing level is necessary if we are somehow to really grasp the 'mechanism' of empathy. In this, we can also see why empathy may be so therapeutic. The feeling of closeness creates trust, a sense that we are being taken care of, and the expectation that things will get better. This lies close to the placebo phenomenon, but there is more. No two people have the same set of subconceptual patterns, since these depend on many factors such as genetic makeup and personal history. However, while not being the same, they may be close enough to each other to allow us to recognize them in other people and communicate deeply with them. This is a hypothesis that should be the subject of further research and validation. In such cases, the difference may give us the opportunity to learn from each other. If someone's patterns are causing them difficulty, then they can learn from another person's patterns and see whether these offer better solutions to life's problems. This is particularly the case when the other person has 'wisdom' – which may be characterized here as having at one's disposal a lot of important mental patterns that can be brought to bear in a natural, 'automatic' way – and is prepared to take the risk of opening themselves up. Note that the second person's conceptual knowledge may be less important than the aforementioned wisdom. Psychotherapy research seems to acknowledge this (cf. *Empathy Beyond the Conceptual Level*).

6.5.3 Empathy and 'Mirror Neurons': The Right Answer to the Wrong Question?

In 1992, 'mirror' neurons were detected in rhesus monkeys. These were a subset of the neurons in the frontal cortex, premotor cortex and inferior parietal cortex that somehow fired when doing a particular action oneself, as well as when the same action was seen as being performed by another monkey (Rizzolatti & Fabbri-Destro, 2010). It was soon proposed that these neurons allow us to detect mental states in others (in other words, empathy) through a process of simulation. This could inappropriately give the impression that empathy is easily explained by the action of a discrete group of neurons, without any 'beyondness'. (Churchland, 2012)

However, mirror neurons are compatible with SP as part of a wide pattern of associations. When a rhesus monkey sees another monkey moving, it doesn't just see a discrete movement of an arm or leg, but instead a complete and detailed

picture of movement within an overall context. Seeing a single movement is not enough to infer a complex social situation or intention. Many elements may be 'mirrored' simultaneously and play a part in comprehending the situation. Neuronal patterns in the motor cortex may be part of the machinery involved in thinking about concrete movements. "*We perceive the actions of others in the same regions that we use to program our own actions.*" (Keysers, 2011, p. 122) The animal apparently uses the same neurons when thinking about their own movement and comprehending the same movement by others. What they do is part of thinking – very generally – about that type of movement, and mirroring comes at no additional cost. Given this, it might be better to drop the term 'mirror'. What this also indicates, at least hypothetically, is that understanding mental state is an activity performed subconceptually within the motor cortex, auditory cortex and so on. Writers such as A. Damasio are elucidating a view of the brain/mind that is much more holistic than previously thought. (Damasio, 2010)

6.6 Subconceptual Processing and Chronic Pain

> SEE ALSO ARTICLE: "SUBCONCEPTUAL PROCESSING: NONSPECIFIC FACTOR OF CHRONIC PAIN"
>
> SEE ALSO CONGRESS ENTRY: "PLACEBO AS COMMUNICATION TO NEUR(ON)AL NETWORKS IN CHRONIC FUNCTIONAL PAIN"

When we experience pain, the amount of neurotransmitters we secrete changes. However, the feeling of pain is not *equivalent to* a change in neurotransmitter levels. It is unimaginable that any chemical substance could *equal* a feeling. Subconceptual processing networks, and especially a combination of these, form a far better candidate.

For example, endorphins are a group of related neurotransmitters that are involved in pain modulation. Nature selected endorphins to play this role in order to influence broad aspects of the way we feel and behave. Pain is one of the most important states for any organism and can be lifesaving, since it draws our attention towards or away from dangerous stimuli. Because of this, it is important that we are able to

modulate our pain state quickly. This goal is achieved by controlling the concentration of endorphins in a wide range of neural networks. Note that endorphin release is not in and of itself the end stage of an analgesic response. When morphine – having a similar action as endorphins in the body – acts on cells and synapses, this has a pain-related meaning because the cells are part of subconceptual processing networks and patterns.

6.7 Subconceptual Processing and Peptic Ulcer Disease

> SEE ALSO ARTICLE: "HELICOBACTER PSYCHOLOGICUS: PSYCHE MEETS BACTERIUM"

Helicobacter pylori has gained acceptance as the main cause of peptic ulcer disease. This may be related to an a priori predilection for bacterium over psyche and for crater over symptoms. However, there are many arguments to put the psyche back on stage alongside the bacterium. According to studies, 'stress' contributes to the etiology of ulcers in many cases (Levenstein, 1998). Also, there is actually a poor correlation between active ulcers and the symptoms of dyspepsia. Furthermore, 40% of patients whose ulcers have healed when examined endoscopically still have persistent symptoms, which are frequently characterized as 'functional' dyspepsia. Note that dyspepsia is comparable to chronic pain, in that it is an *interpretation* by the mind of what is happening in the body. As with any feeling, it is influenced at the subconceptual level by many affective and cognitive factors before it is felt consciously.

The emphasis on material causes in peptic ulcer disease is one example of the unease that exists in medicine when it comes to 'deeper meaning'. Of course, the consequences of this are enormous. The issue is that the heavy emphasis on the ability to conceptualize things devalues the role of the subconceptual. Hopefully, the subconceptual processing paradigm will make it clear that 'deeper meaning' is also firmly rooted in the material, rather than being something merely 'ethereal' and therefore to be discarded.

6.8 Subconceptual Processing and Epilepsy

> SEE ALSO ARTICLE: "PSYCHE, SOMA AND SEIZURES: MIND-BODY NON-DUALISM CHANGES THE WHOLE PICTURE"

The domain of seizures is still plagued by Cartesian dualism. As a direct consequence, seizures are largely classified as organic, psychogenic, or of mixed nature and are treated as such. However, in *Psyche, Soma and Seizures*, we contend that *functional* ES and PNES do not lie on opposite sides of the dividing line between mind and brain since that line does not exist, but instead form a continuous spectrum with a common etiology. Looking at seizures from a non-Cartesian standpoint – where the mind and brain are one – the only chasm that needs to be crossed is an EEG phenomenon that may simply be a coping mechanism, similar to a fever in someone with an infection, rather than a direct reflection of the underlying disorder.

With ES and PNES, EEG phenomena are used to *make* a theoretical distinction between the two conditions, and then are used *as proof of* the existence of that distinction. This shows that the distinction may well exist only by convention, since it is a logical fallacy to distinguish between two things based on a convention that defines that distinction. This is equivalent to looking at a disease that sometimes causes a fever, and saying that there are two different diseases – one that causes a fever and one that does not. The fact that many accept ES and PNES as different conditions may be a symptom of the persistent prevalence of Cartesian dualism, where the mind and body are seen as fundamentally different.

Contrary to this, SP shows that mind and body are fundamentally the same. Taking the SP perspective, the domain of epilepsy may enter a new landscape where dualistic borders become very fuzzy – there is no underlying need to prove the existence of a chasm. Furthermore, SP and epilepsy are tightly related, since they are both about neurons firing either in concert or chaos, and things happening in the brain that are beyond voluntary control. However, they are not completely beyond control: people can avert or bring on seizures depending on whether or not they make a specific mental effort to relax. Subconceptual processing, in being a bridge between psyche and soma – or showing that they overlap – is bound to show how people with PNES can be helped further, and even those with ES may be helped. (Auto)suggestion as an aspect of subconceptual communication will probably play a

central role in this. As an additional benefit, the need for relatively toxic antiepileptic medications may diminish to a substantial degree.

At the same time, this may help us to learn a lot more about mental disorders such as schizophrenia, where there is clearly a deficit at the subconceptual pattern level.

6.9 Subconceptual Processing and Myocardial Ischemia

> SEE ALSO ARTICLE: "THE CHOKED HEART AND HOW TO RELEASE IT"

When we take into account the potential impact of SP on health, as well as related intricacies of medical causal thinking, we become more sensitive to the possible impact of concrete mental patterns on concrete medical issues. One example of this is the pattern of oppression that is felt by many patients with myocardial ischemia. If the mind and body are seen as separate, the 'deeper meaning' of oppression would seem unlikely to be able to influence something as material and specific as coronary arteries. However, from a SP viewpoint where the mind and body are unified, such an influence appears much more plausible – although it is not immediately evident that this is the case.

Several things give weight to the hypothesis that a mental pattern of oppression can indeed lead to myocardial ischemia and even myocardial infarction. These include epidemiological data, personal susceptibility factors, the pathophysiological mechanism of large and small coronary artery spasms, and the existence of the related Japanese tako-tsubo syndrome. Other related mind/body phenomena give further weight to the hypothesis, including everyday blushing and erections. However this picture may be complicated by the fact that coronary artery spasms may coexist with coronary atherosclerosis.

If this hypothesis is true, then we may be able to manage coronary vasospasm and angina using pattern-related strategies, such as autosuggestion exercises that are designed to help the sufferer release their coronary arteries and 'open up' more generally. With the use of such exercises, this hypothesis can be put to a simple test.

Mental patterns, deeper meaning and SP lie at the core of this issue. If the hypothesis proves to be correct, the search may be on for many more causal mechanisms that involve mental patterns. This may result in a significant number of

causal insights across diverse domains, and may also suggest ways of managing or even preventing a number of medical conditions for which there is currently no effective treatment.

6.10 Subconceptual Processing and 'Healing Methods'

> SEE ALSO ARTICLE: "FROM "DOES IT WORK?" TO "WHAT IS 'IT'?" – IMPLICATIONS FOR CAM, VOODOO, PSYCHOTHERAPY, POP-PSYCHOLOGY AND REGULAR MEDICINE"

Increasingly, people think that if a health-related procedure works, then we should just use it. However, very little thought goes into precisely what it is that 'works'. Following this reasoning, and given the strength of empathy and the placebo effect, anything can pass the test and 'work'. However, there are several significant drawbacks to adopting this approach. These include the hidden side effects of concealed placebo use, temporary improvement of symptoms followed by further deterioration, obstacles to scientific progress, and the lost opportunity for personal growth. It also creates the dangerous impression that anything, no matter how irrational, can easily gain credence, and that rationality itself has little value in healthcare. In addition, healing methods that do not take SP into account are covert in nature, and therefore do not provide sustainable solutions.

SP provides a complete explanation of why healing methods work. Therefore, SP should be seriously considered before any other explanation. The question is not whether there is a valid explanation, but instead whether SP offers a better explanation with more supporting evidence. Patients want something that 'works', but they also do not want to be consciously or unconsciously deceived by practitioners, or by institutions that historically and socio-politically are supposed to be beacons of trustworthiness. Particularly in healing methods, we can see the remnants of magical thinking, which we need to eliminate completely over time.

The main way of accomplishing this in the long term may be by turning to SP. This is where deeper meaning resides, including the meaning of life and that ultimate sense of being that we have historically called the soul. SP offers a completely open

approach to understanding the depth of human feelings, letting us approach them scientifically.

7 Strengths, Weaknesses and Opportunities

7.1 Strong Points of This Thesis

Deeper meaning is important. This has been known intuitively for a very long time, and yet we still lack many of the scientific tools needed to conduct verifiable and falsifiable research in this area. Further theoretical analysis is needed, and – wherever possible – much experimental research.

With this PhD, we have developed a foundation for theoretical advances by crossing over from the purely medical domain into the area of cognitive neuroscience. This is now a mature and consolidated area of science with several decades of history and extensive high-quality research. We have created a much-needed synthesis that can serve as a permanent bridge between these domains. To the best of our knowledge, this has not been done previously.

We have approached this in very broad terms, bringing in domains that include medical causal thinking, placebo, empathy, evidence-based medicine and healing methods, as well as addressing a number of specific areas of healthcare such as PUD, PNES and chronic pain. In doing this, we have drawn upon a body of theory and empirical knowledge that is both robust and encompassing.

We have conducted extensive searches of peer-reviewed Pubmed literature across numerous areas of study, distilling a vast volume of existing research into our own. In doing this, we have found that a significant amount of medical knowledge is congruent with our own theories, while we have not found any that clearly contradicts them. In addition, our research in several domains has yielded results that are internally consistent to a high degree. Taken as a whole, we have created a self-consistent body of knowledge with central concepts that do not suffer any major contradictions. In addition to answering many questions, we have also laid the basis for answering many more through future research that builds on this foundation.

7.2 Weak Points

In order to understand subconceptual processing better, the activity of many millions of individual neurons needs to be recorded simultaneously. From a technical standpoint this is not currently feasible, making subconceptual processing somewhat of a gray area. Although we already know quite a lot, and can take a relatively fine-grained internal view of the brain, the future still has a lot more to reveal.

Experimental research that fully embraces the importance of subconceptual processing is still lacking in many medical domains. We have only highlighted a few significant ones, and developing a full account will require much future research by ourselves and other parties.

Due to resource constraints, we have made no attempt to discuss our ideas with global thought leaders. We will strive to do so in print, via email and through conference attendance. We are planning an international conference on empathy where we intend to invite some of these leaders.

This research involves several fuzzy concepts, including placebo and empathy. These terms mean different things to different people, although we did our best to define these as clearly as possible for the purposes of this thesis text and the articles that form part of this thesis.

Concrete management of conditions based upon subconceptual processing methods is only slightly discussed in this text and in the articles. This was not one of our objectives. At first, we started to carry out research with this goal in mind, but we had to abandon it due to a lack of resources. We do think that this type of research is immensely important and hope that this thesis will make such research possible.

7.3 Directions Towards Future Research and Practical Enhancement of Healthcare

In view of the insights in this thesis and the implications of these, we advocate initiatives in the following areas:

- **More specific scientific research into the placebo phenomenon** is needed, including into its potential side effects (see *Placebo Side Effects*). The use of placebos in a deceptive manner will not be sustainable in future both from a deontological and medico-legal perspective. Patient consent will become an insurmountable barrier, as it will be considered a basic patient right. However, given that placebos, open-label placebos and complete openness lie along a continuum (see *Open Placebo*), this change can occur gradually. Research should therefore also focus on how to best manage these issues in a seamless and timely manner, avoiding the need for abrupt and disruptive decisions down the road.

- **Significant emphasis on 'empathy beyond' research** is also recommended. The potential and complexity of empathy are both vastly underestimated at present. We are currently organizing a worldwide 'Empathy for Health' congress in April 2015, with the goal of soliciting a significant worldwide contribution in this area. Sponsorship is welcome.

- The framework elucidated in this thesis opens up the possibility of **the use of autosuggestion as a research tool in many healthcare domains.** As a complement to this thesis, a large number of these practical tools have been developed for approximately 200 wellness and healthcare topics. These are available for both experimental use and patient management. This approach holds out the promise of cost-effective and sustainable solutions to a wide range of concrete health-related issues – such as chronic pain management. These tools are available on the Internet, and therefore research can also be Internet-based – eliminating many logistical burdens, as has already been investigated in the PALPI study of chronic pain.

- It is becoming increasingly practical to **use neuroimaging to investigate the influence of autosuggestion on the brain and on health outcomes** across a wide spectrum of conditions. For instance, neuroimaging studies can be carried out prior to treatment and then again 3 to 6 months later in order to track visible changes.

- We advocate specific research into how the concepts established in this thesis bring **new insights to otherwise intractable problems in the area of CAMs**. As discussed in the article *From "Does it work?" to "What is 'it'?"*,

CAMs are a diverse set of healing methods with little or no scientific underpinning. However, the main reason that people engage in CAMs is that scientific medicine does not offer effective solutions for many health problems – particularly in the long term. Additionally, many people intuitively understand that the solution to their health problems lies within themselves. Management approaches that are consistent with the principles laid out in this thesis may therefore address people's expectations while still adhering to scientific tenets.

- We also recommend **research into the common factors that underpin both empathy and healthcare and leadership in 'openness'**. Many parallels exist, such the enormous importance of motivation – including in areas such as safe work behavior, taking medication, quitting smoking and not overeating. This will further the aim of having healthier people and healthier institutions within a healthier society.

- **International research consortia** can make these research outcomes relevant to international audiences. They also make it possible to explore cultural differences in the way that people respond to treatments based on the principles established in this thesis, as well as the cultural impacts of widespread adoption of these approaches.

From the subconceptual processing perspective, the *patient is the cure*. Therefore, patients can accomplish significant things by themselves, provided that they have all the necessary external support. Instead of being a helpless recipient of external cures, patients can learn to rely on themselves and grow personally in the process. We know that many psycho-somatic issues are engendered by *learned helplessness*. In this sense, an external 'cure' can create future problems. With the *patient as cure*, this can be avoided. This transition is actually very much in line with many people's desires.

8 General Conclusions and Broad Perspectives

> "*In his thoughts, to be sure, the physician can abstract body from mind and consider it separately in order to be less confused in the marshalling of ideas. But in the actual practice of his art, where he has to do with man as he is, should the physician devote all of his efforts to the body alone and take no account of the mind, his curative endeavors will pretty often be less than happy and his purpose either wholly missed or part of what pertains to it neglected.*" – Jerome Garb, 1747 (Rather, 1965, p. A84/64)

8.1 Deeper Meaning and Medical Science

In order to be clear-cut, experimental science needs clear-cut concepts. Of course, this poses an intrinsic problem when it comes to 'deeper meaning', where being clear-cut is not feasible. A person is often not aware of much of the 'deeper meaning' in themselves. In other cases, they may feel the meaning but cannot identify its exact source. Unfortunately, this domain is not very susceptible to *experimental* science. We have to acknowledge that present-day experimental science is incapable of going very deep into our psyche. However, just because something cannot readily be proven does not mean that it is unimportant. For instance, when asking the question whether psychological influences on cancer initiation and progression are real, science looks for clear-cut concepts, and in doing so bypasses 'deeper meaning'. Nevertheless, *if* the psyche has any influence on cancer, then this must be sought where 'meaning' is most relevant, and at the same time closely associated with the body.

The types of beliefs that apply in this domain are not ones such as "I believe it will rain tomorrow.", but instead ones such as "I truly and deeply believe that I can get

better, and that my life will have purpose and deeper meaning after I am eventually cured." In future, science should investigate this deeper meaning as much as possible. Appropriate questionnaires should be developed to probe this. If important depths are not explored, then clear-cut but superficial concepts will be confused with deeper meaning. Experiments that make use of these superficial concepts are fatally flawed, and a priori they will not show clear correlations.

However, if we see that experimental science is *in principle* not a good way of approaching a domain, then we should not just leave that domain as a void to be filled by anything or anyone, such as a 'healer' who wants to defraud desperate and gullible people.

The analogy of a computer is helpful, in that by looking at a modern computer, we can see what the human mind is *not*, although it may appear to be so at first glance. The most important differences between them may arise from the fact that 'hardware' and 'software' are not distinct in the human mind/brain, unlike a digital computer.

Deeper meaning, much like consciousness, 'emerges' from a vast network of intertwined networks. Ultimately, these form an enormously vast 'parallel distributed network' consisting of neurons, synapses, dendrites and so on. This in turn shows us how to think about deeper meaning, what we can expect from it, how to communicate with it, and how it can be 'invited' to work towards better health and well-being, and the realization of human endeavors and potentials.

8.2 Main Implications for the Future of Healthcare

Today's scientific medicine is not yesterday's, nor is it tomorrow's. How different it will be in the future we do not know. Almost certainly, the future view of the human mind/brain will play a large role in how future medicine is shaped. To disregard the subconceptual level in order to avoid 'magic' is itself an irrational stance, particularly as much present-day knowledge points to its importance. So, we have to ask the question once again: "Which framework is the most appropriate for the future evolution of scientific medicine?"

Clearly, a purely conceptual framework lends itself readily to experimental medicine. This approach allows clear-cut experiments to be performed relatively

easily under controlled conditions. This is acceptable in domains where the conceptual framework closely parallels reality, such as in the laboratory or in the emergency department.

A subconceptual framework, however, is more appropriate in many circumstances, and particularly in the field of psycho-somatics, where the reality of the human mind needs to be fully taken into account. To constrain reality to that which can be experimentally investigated at a conceptual level simply disregards the importance of subconceptual processing. Given our present level of knowledge, we are not entitled to do this. Amongst other things, the placebo effect shows us this importance. It is also highlighted by the continuing failure of medical knowledge extraction in the area of expert systems, mainly due to the generally acknowledged fact that medical knowledge is only partially formalizable. Yet another example is medical empathy, which is "needed even when it is quite obvious what emotional label applies to a patient" (Halpern, 2003, p. 671), and therefore transcends the purely conceptual level.

If somehow we reach the conclusion that it doesn't matter how a patient gets better – whether that be through drugs or deeper meaning – then we will have reverted to 'magical thinking', pretending to wield a power that we do not possess, and which actually lies within our patients (Frank, 1973). At this point, science stops. This would have a tremendous impact, both in terms of financial cost and human suffering.

8.3 Empathy and autosuggestion

"*If everything were known about the etiology of the placebo effect, the terms placebo and placebo effect would disappear and be replaced by a hugely powerful megapsychotherapy.*" (Shapiro & Shapiro, 1997, p. 29)

A clear distinction between 'empathy beyond' and 'placebo as deception' allows us to posit practical, therapy-oriented consequences. Specifically, the 'megapsychotherapy' from the quote above may well involve a combination of 'empathy beyond' and proper use of autosuggestion. In this model, the therapist or caregiver provides an optimal combination of 'empathy beyond' and autosuggestion support to the patient. The patient or client can then use autosuggestion by themselves, or in combination with support when needed.

Clearly it is not the placebo that works, but instead the accompanying suggestion(s). These suggestions can be verbal, as in "This pill works." They can also be non-verbal – for instance, when the patient makes the implicit assumption that pills almost always work. It is these suggestions that provide hope, meaning and expectation. They can also be regarded as patterns that overlap with patterns that are already present in the mind/body of the patient. It is this overlap that creates the connection and the ensuing placebo effect that is manifested in the brain and other parts of the body. Viewed from this perspective, it becomes apparent how this overlap can be accomplished in more direct ways without the need for a deceptive placebo. Verbal autosuggestion is a prime example of this – and can, for instance, take the form of prerecorded autosuggestion sessions as it did in the PALPI study.

An important difference between most traditional psychotherapy and 'empathy beyond' is that the therapist does not employ any techniques to change the patient with 'empathy beyond' – the only technique used during the encounter is empathy and the only instrument is the therapist. Techniques can be used to heighten the empathy. They are oriented towards the therapist, not towards the client. Techniques are specifically not used towards controlling the client, nor the client's symptoms, in an exclusively conceptual manner. The therapist then advises the patient about which autosuggestion tools to use. In this approach, the therapist is more like a gardener than a mechanic, and the process for the patient is more of a path than a cure. The overall metaphor is natural, organic growth rather than an artificial remedy.

To the degree that this approach really provides an effective way of dealing with many health and healthcare issues, obviously it is important to consider its ethical implications. Since it acts on the most important aspects of what it is to be a human being, not just any use of empathy and autosuggestion is acceptable. For instance, psychopaths can be regarded as 'empathic' in the way that they understand what makes others suffer – a knowledge that they use to accomplish their perverted goals. Therefore, the use of autosuggestion tools needs to involve high ethical principles. The 'user' (client, patient or other) cannot be expected to make an in-depth evaluation of various different developments in the field, and therefore therapies need to be approved based on ethical principles.

We suggest that there are five of these principles: openness, freedom, depth, respect and trustworthiness. All of the relevant principles can easily be derived from these. These five principles overlap to some extent, which is necessary in order for

them to be comprehensive. They are also complementary, in that each of them obtains its full meaning when viewed in the light of the others. To demonstrate the relevance of these principles, it is clear that the deceptive use of placebos violates all of them.

There is an ongoing discussion about whether placebos should be used for the sake of being humane. In other words, if we only have a placebo to alleviate symptoms, then should we use it? It is hoped that this thesis shows that the use of placebo should be avoided in all but extreme circumstances, and that alternatives should be investigated whenever possible. It is our belief that a proper combination of empathy and autosuggestion provides a perfect alternative that hopefully will be widely employed in future.

8.4 Afterword

Scientific medicine is destined to enter into a new paradigm, one that can already be found in the *appearance* – but not the reality – of some alternative medicines. We would do well to acknowledge the real need that lies behind this, and to embrace it within scientific medicine instead of abandoning it to shamans. In this regard researchers such as M.R. Rajagopal (Rajagopal, 2006) view functional pain and other similar suffering as possibly only the tip of the iceberg. When this pain is relieved, the patient feels better, but other pains or symptoms surface. M. Kearney (Kearney, 1996) talks of 'superficial work' that tackles the tip of the iceberg, and 'depth work' that takes into account a broader picture.

The real 'cause' of chronic functional suffering probably lies in self-perpetuating patterns where elements mutually enhance each other. These elements include physical causes such as disuse, deconditioning, overstretching and repetitive traumata, as well as mental, emotional and social ones. The latter categories include pain, anxiety, hypervigilance, relational problems, negative affects, negative interpretations, 'growth', many different social interactions, and even excessive investment in material causes and treatments. Existential suffering – where pain is a symbol for much wider life experiences – also plays a role, as does a belief that pain is indicative of underlying diseases. Any pain, whether it is acute or chronic, is a call for attention. In the case of chronic pain, attention is sought for deep underlying needs. This is more of a 'path' than a cry for treatment in the

conventional sense. When the path is not entered, the pain calls harder and harder, and really starts to 'hurt'.

'Inner strength' seems to lie behind the placebo effect. It is wrong to leave this truth hidden, if only because this increases people's vulnerability to others who seek to deceive them. In addition, treating a placebo as some type of black box clearly hampers scientific progress. Lastly, medical science needs to become more skeptical about itself. Double-blind RCTs lie at the heart of evidence-based medicine, but are at present based on a rather questionable relationship with placebos.

As a society, we are engaged in an ongoing battle with chronic functional suffering. Despite this, chronic suffering is at historic highs. The main reason for this may be that the role of subconceptual processing in chronic suffering is not acknowledged. In a primitive society, people naturally live a symbolic life where they are in contact with their inner selves – in other words, they embrace the subconceptual. In our sophisticated modern society, which is becoming more and more prevalent globally, technology offers many other possibilities and therefore we risk losing contact with our inner selves.

Only truth can truly cure. Not only can it make people better from a symptomatic perspective, it also offers a path towards positive personal development. Therefore, while the placebo effect is indeed real, the important question is *what* works. Clearly, what works is the 'inner strength' of the recipient, and specifically the enormous potential that lies within their subconceptual processing capacity. Another question that is incredibly important is *towards what end.* If our only goal is to alleviate chronic suffering as quickly as possible, that leaves a number of crucial questions unanswered, such as "*Why* is there chronic functional suffering?" and even ultimately, "What is the purpose of being?"

9 Bibliography of Introduction, Discussions, Conclusions and Addendum

Ahn, H. N., & Wampold, B. E. (2001). Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. *J Couns Psychol, 48*, 251-257.

Aisbett J., Gibbon G. (2001). A general formulation of conceptual spaces as a meso level representation. *Artificial Intelligence*, 133, no. 1-2.

Amanzio, M., & Benedetti, F. (2006). (1999) Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific sub-systems. *J Neurosci, 19*, 484–494.

Anderson, J. R., & Bower, G. H. (1973). *Human associative memory.* Washington: Winston and Sons.

Banja, J. D. (2006). Empathy in the physician's pain practice: benefits, barriers, and recommendations. *Pain Med, 7*, 265-275.

Batson, C. D., Batson, J. G., Slingsby, J. K., Harrell, K. L., Peekna, H. M., & Todd, R. M. (1991). Empathic joy and the empathy-altruism hypothesis. *J Pers Soc Psychol*, 413-426.

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2007). *Neuroscience – Exploring the Brain.* Philadephia: Lippincott Williams & Wilkins.

Bechtel, W., & Abrahamsen, A. (2002). *Connectionism and the mind.* Oxford: Blackwell Publishers.

Benedetti, F. (1996). The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain, 64*, 535–543.

Benedetti, F., & Arduino, C. (1999). Somatotopic activation of opioid systems by target-directed expectations of analgesia. *J Neurosci, 19*, 3639–3648.

Benedetti, F., Amanzio, M., Vighetti, S., & Asteggiano, G. (2006). The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J Neurosci, 26*, 12014–12022.

Benedetti, F., Lanotte, M., Lopiano, L., & Colloca, L. (2007, Jun). When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience, 147*(2), 260-71.

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor and hormonal placebo/nocebo responses. *J Neurosci, 23*, 4315–4323.

Bode, S., He, A. H., Soon, C. S., Trampel, R., Turner, R., & Haynes, J. D. (2011). Tracking the unconscious generation of free decisions using ultra-high field fMRI. *PLoS One, 6*(6), e21612.

Bornstein, R. F. (1992). Subliminal mere exposure effects. In R. F. Bornstein, & T. S. Pittman (Eds.), *Perception without awareness: cognitive, clinical and social perspectives* (pp. 191-210). New York: Guilford.

Bowers, K. S., Regehr, G., Balthazard, C., & Parker, K. (1990). Intuition in the context of discovery. *Cognitive Psychol, 22*, 720-110.

Bowlby, J. (1969) *Attachment*. London: Pelican.

Bucci, W. (1997) *Psychoanalysis and Cognitive Science*. New York: Guilford Press.

Buchgreitz, L., Lyngberg, A. C., L, B., & Jensen, R. (2006). Frequency of headache is related to sensitization: a population study. *Pain, 123*, 19-27.

Bunge, M. (2007). Blushing and the philosophy of mind. *J Physiol Paris, 101*, 247-256.

Chella A. (1999). Symbolic and Subsymbolic Representations: an Artificial Vision Framework. In V. Cantoni et al. (eds.), *Human and Machine Perception 2: Emergence, Attention, and Creativity.* Boston: Kluwer Academic Publishers.

Churchland, P. S. (2002). *Brain-Wise, Studies in Neurophilosophy.* Cambridge: MIT Press.

Churchland, P. S. (2012). *Braintrust: what neuroscience tells us about morality* (Reprint edition ed.). Princeton: Princeton University Press.

Churchland, P.S., Sejnowski T.J. (1992). *The Computational Brain*. Cambridge: The MIT Press.

Cleary, A. M. (2006). Relating familiarity-based recognition and the tip-of-the-tongue phenomenon: detecting a word's recency in the absence of access to the word. *Mem Cognit, 34*(4), 804-16.

Clyman, R. (1991). "*The procedural organization of emotions*" in T.Shapiro and R.Emde (eds) *Affect, Psychoanalytic Perspectives*. New York: International Universities Press.

Damasio, A. (2010). *Self comes to mind: constructing the conscious brain.* New York: Pantheon.

De Pascalis, V., Chiaradia, C., & Carotenuto, E. (2002, Apr). The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. *Pain, 96*(3), 393-402.

Demos, K. E., Kelley, W. M., Ryan, S. L., Davis, F. C., & Whalen, P. J. (2008). Human amygdala sensitivity to the pupil size of others. *Cereb Cortex, 18*, 2729-2734.

Dennett, D. C. (1992). *Consciousness explained.* London: The Penguin Press,.

Duncan, G. (2000). Mind-body dualism and the biopsychosocial model of pain: what did Descartes really say? *J Med Philos, 25*, 485-513.

Evans, F. G. (1985). Expectancy, therapeutic instructions, and the placebo response. In L. White, B. Tursky, & G. E. Schwartz (Eds.), *Placebo: Theory, Research and Mechanisms* (pp. 215–228). New York: The Guilford Press.

Eysenck, H. J. (1991). Is suggestibility? In J. F. Schumaker (Ed.), *Human suggestibility. Advances in theory, research and application* (pp. 76– 90). New York: Routledge.

Fodor, J. A. (1983). *The Modularity of Mind.* Cambridge: MIT Press.

Frank, J. D. (1973). *Persuasion and healing.* Baltimore: Johns Hopkins University Press.

Fuchs E., Flugge G., Czeh B. (2006) Remodeling of neuronal networks by stress. Front. Biosci., 11:2746-58.

Gärdenfors P. (1997). Symbolic, Conceptual and Subconceptual Representations. In V. Cantoni et al. (Eds.), *Human and Machine Perception*. New York: Plenum Press.

Gazzinaga, M. S. (Ed.). (2009). *The Cognitive Neurosciences.* Cambridge: The MIT Press.

Gerhardt, S. (2004). *Why Love matters – How Affection Shapes a Baby's Brain*. London & New York: Routledge.

Ghiselin, B. (1952). The creative process. 37-40. New York: New American Library.

Goubert, L., Craig, K. D., Vervoort, T., Morley, S., Sullivan, M. J., de C Williams, A. C., . . . Crombez, G. (2005). Facing others in pain: the effects of empathy. *Pain, 118*, 285-288.

Halpern, J. (2003). What is clinical empathy? *J Gen Intern Med, 18*, 670-674.

Hashish, I., Harvey, W., & Harris, M. (1986). Anti-inflammatory effects of ultrasound therapy: evidence for a major placebo effect. *Br J Rheumatol, 25*, 77-81.

Hassan, S., Karpova, Y., Baiz, D., Yancey, D., Pullikuth, A., Flores, A., . . . Kulik, G. (2013). Behavioral stress accelerates prostate cancer development in mice. *J Clin Invest, 123*, 874-886.

Haynes, J. D., & Rees, G. (2005). Predicting the stream of consciousness from activity in human visual cortex. *Curr Biol, 15*(14), 1301-1307.

Heil, J. (2004). *Philosophy of Mind – a contemporary introduction.* New York: Routledge.

Hein, G., & Singer, T. (2008). I feel how you feel but not always: the empathic brain and its modulation. *Curr Opin Neurobiol, 18*, 153-158.

Hirst G., Edmonds P. (2002). Near-synonymy and subconceptual similarity. ftp://ftp.cs.toronto.edu/public_html/cs/ftp/pub/gh/Hirst+Edmonds-97.ps

Hrobjartsson, A., & Gotzsche, P. C. (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med, 344*, 1594-1602.

Hunter, P. (2007). A question of faith. Exploiting the placebo effect depends on both the susceptibility of the patient to suggestion and the ability of the doctor to instill trust. *EMBO Rep, 8*, 125-128.

Jacobs, R. A., Jordan, M. I., & Barto, A. G. (1991). Task decomposition through competition in a modular connectionist architecture: the what and where vision tasks. *Cognitive Sci, 15*, 219-250.

James, W. (1985). *The varieties of religious experience.* New York: Penguin Classics.

Kearney, M. (1996). Mortally wounded. 66-67. New York: Simon & Schuster.

Kessler K., Duwe I., Strohner H. (1999). Grounding Mental Models: Subconceptual Dynamics in the Resolution of Reference in Discource. In G.Rickheit, C.Habel (Eds.), *Mental Models in Discource Processing and Reasoning.* Amsterdam: Elsevier Science B.V.

Keysers, C. (2011). *The empathic brain.* Social Brain Press.

Kirsch, I. (2005). Placebo Psychotherapy: Synonym or Oxymoron? *J Clin Psychol, 61*, 791-803.

Kirsch, I. (2009). *The emperor's new drugs.* London: The Bodley Head.

Koshi, E. B., & Short, C. A. (2007, Mar). Placebo theory and its implications for research and clinical practice: a review of the recent literature. *Pain Pract., 7*(1), 4-20.

LeDoux, J. (2002). *The Synaptic Self – How Our Brains Become Who We Are.* London: Penguin Books.

Levenstein, S. (1998). Stress and peptic ulcer: life beyond helicobacter. *BMJ, 316*, 5385-41.

Levine, J. D., & Gordon, N. C. (1984). Influence of the method of drug administration on analgesic response. *Nature, 312*, 755–756.

Martin K.A.C. (2002). The Microcircuits of Visual Cortex. *Current Opinion in Neurobiology*, 12:418–425.

Mathiasen, H. (2006). Empathy and sympathy: voices from literature. *Am J Cardiol, 97*, 1789-1790.

Mayer, E. A., & Bushnell, M. C. (Eds.). (2009). *Functional pain syndromes.* Seattle: IASP Press.

Melzack, R., & Wall, P. D. (Eds.). (2008). *Handbook of Pain Management.* London: Churchill Livingstone.

Merleau-Ponty, M. (1964). *The primacy of perception.* Boston: Northwestern University Press.

Metzinger T. (2000). The Subjectivity of Subjective Experience. In T.Metzinger (Ed.). *Neural Correlates of Consciousness: Empirical and Conceptual Questions*. Cambridge: MIT Press.

Moray, N. (1950). Attention in dichotic listening: affective cues and the influence of instructions. *Q J Exp Psychol A, 11*, 56-60.

Niedenthal P.M., Kitayama S. (1994). *The Heart's Eye.* San Diego: Academic Press.

Pascual-Leone A. (2009). Characterizing and Modulating Neuroplasticity of the Adult Human Brain. In M.S.Gazzinaga (Ed.), *The Cognitive Neurosciences*. Cambridge: The MIT Press.

Plotkin, W. B. (1985). A psychological approach to placebo: the role of faith in therapy and treatment. In L. White, B. Tursky, & G. E. Schwarts (Eds.), *Placebo: theory, research and nechanisms.* New York: Guilford Press.

Price, D. D., & Fields, H. L. (1997). The contribution of desire and expectation to placebo analgesia: implications for new research strategies. In A. Harrington (Ed.), *The placebo effect - an interdisciplinary exploration.* London: Harvard University Press.

Price, D., Milling, L. S., Kirsch, I., Duff, A., Montgomery, G. H., & Nicholls, S. S. (1999). An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain, 83*(2), 147-156.

Put, C., Van den Bergh, O., Van Ongeval, E., De Peuter, S., Demedts, M., & Verleden, G. (2004). Negative affectivity and the influence of suggestion on asthma symptoms. *J Psychosom Res, 57*(3), 249-255.

Rajagopal, M. R. (2006). Pain and beyond. *Indian J Palliat Care, 12*, 4-7.

Rantala V. (2002). *Explanatory Translation: Beyond the Kuhnian Model of Conceptual Change*. Boston: Kluwer Academic Publishers.

Rather, J. L. (1965). *Mind And body in eighteenth century nedicine: a study based upon Jerome Garb's de regimine mentis.* Berkeley: University of California Press.

Rizzolatti, G., & Fabbri-Destro, M. (2010). Mirror neurons: from discovery to autism. *Exp Brain Res, 200*, 223–237.

Rossi, E. L., & Rossi, K. L. (2007). What is a suggestion? The neuroscience of implicit processing heuristics in therapeutic hypnosis and psychotherapy. *Am J Clin Hypn, 49*(4), 267-281.

Rueckl, J. G., Cave, K. R., & Kosslyn, S. M. (1989). Why are ``what'' and ``where'' processed by separate cortical visual systems? A computational investigation. *J Cognitive Neurosci, 1*, 171-186.

Rumelhart, D. E., & McClelland, J. L. (1986). *Parallel Distributed Processing.* Cambridge: MIT Press.

Schummers J., Mariño J., Sur M. (2004) Local networks in visual cortex and their influence on neuronal responses and dynamics. J Physiol Paris, 98(4-6), 429-41.

Shapiro, A. K., & Shapiro, E. (1997). *The powerful placebo.* Baltimore: The Johns Hopkins University Press.

Sidis, B., & James, W. (1919). *The psychology of suggestion : a research into the subconscious nature of man and society.* New York: Appleton.

Simon, D. J., & Chabris, C. F. (1999). Gorillas in our midst: sustained inattentional blindness for dynamic events. *Perception, 28*, 1059-1074.

Sloan, E. K., Priceman, S. J., Cox, B. F., Yu, S., Pimentel, M. A., Tangkanangnukul, V., . . . Cole, S. W. (2010). The sympathetic nervous system induces a metastatic switch in primary breast cancer. *Cancer Res, 70*, 7042-7045.

Smolensky P. (2000). Connectionism and the Foundations of AI. In R.Chrisley, S.Begeer. (Eds.) *Artificial Intelligence: Critical Concepts*. London: Routledge.

Smolensky, P. (1988). On the proper treatment of connectionism. *Behav Brain Sci, 11*, 1-74.

Smolensky, P. (1988). On the proper treatment of connectionism. *Behavioral and Brain Sciences*, 11, 1-74

Soon, C. S., Brass, M., Heinze, H. J., & Haynes, J. D. (2008). Unconscious determinants of free decisions in the human brain. *Nat Neurosci., 11*(5), 543-545.

Spiegel, H., & Spiegel, D. (2004). *Trance and treatment – clinical uses of hypnosis.* Arlington: American Psychiatric Publishing.

Stern, D. (1985) *The Interpersonal World of the Infant.* New York: Basic Books.

Sugu D., Chatterjee A. (2012). Affective Information Processing and Representations. In Malay K. Kundu, Sushmita Mitra, Debasis Mazumdar, Sankar K. Pal (Eds.), *Perception and Machine Intelligence: First Indo-Japan Conference.*

Sun, R. (1994). An introduction: On Symbolic Processing in Neural Networks. In R. Sun, L.A. Bookman (Eds.), *Computational Architectures Integrating Neural and Symbolic Processes*. Boston: Kluwer Academic Publishers.

Thompson, J. J., Ritenbaugh, C., & Nichter, M. (2009). Reconsidering the placebo response from a broad anthropological perspective. *Cult Med Psychiatry, 33*, 112-152.

Turk, D. (2004). Understanding pain sufferers: the role of cognitive processes. *Spine J, 4*(1), 1-7.

Vase, L., Riley, J. L., & Price, D. D. (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia - Table 3. *99*, 443-452.

Verhaeghe, P. (2009). *Het einde van de psychotherapie.* De bezige bij.

Waber, R. L., Shiv, B., Carmon, Z., & Ariely, D. (2008). Commercial features of placebo 1 and therapeutic efficacy. *JAMA, 299*, 1016-1017.

Wampold, B. E. (2001). Contextualizing psychotherapy as a healing practice: culture, history and methods. *Appl Prev Psychol, 10*, 69-86.

Wampold, B. E., Imel, Z. E., & Minami, T. (2007). The placebo effect: "relatively large" and "robust" enough to survive another assault. *J Clin Psychol, 63*, 401-403.

Wampold, B. E., Minami, T., Tierney, S. C., Baskin, T. W., & Bhati, K. S. (2005). The placebo is powerful: estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *J Clin Psychol, 61*, 835-854.

Wegner, D. M. (2002). *The illusion of conscious will.* Cambridge: MIT Press.

Zeki, S. (1993). *A vision of the brain.* Oxford: Blackwell.

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11 Addendum

Relevant Cognitive Neuroscience Quotes

These are a number of quotes – not otherwise included in the thesis – about the subconceptual literally, followed by quotes about neur(on)al networks and activation patterns:

- *On the side of what is represented, the conceptual level is populated by consciously accessible concepts, whereas the subconceptual level is comprised of fine-grained entities beneath the level of conscious concepts. For connectionist models the conceptual level consists of patterns of activity over many units and their interactions; the subconceptual level consists of individual units and their interconnections.* (Smolensky, 1988, p.63)

- *Concepts can be thought of as stable activational states in a connectionist network, which satisfy the maximal number of referential constraints by the amount of subconceptual overlap between verbal and visual information. Computer simulations with a connectionist network give insight into the subconceptual dynamics which may ground mental models… The results were as follows: Referential relationships could be very well predicted by the subconceptual overlap between nouns and objects. The degree of conceptual relationships determined by subconceptual overlap had a significant effect on the referential reaction times.* (Kessler, Duwe & Strohner, 1999, p.171; 187)

- *The subconceptual level is a semantic level at which the activities of individual units in a connectionist system (and possibly units in subsymbolic systems of other kinds) are given a semantic content. Here the semantic content of a unit is microfeature of something; it is a subconcept rather than concept.* (Rantala, 2002, p.153)

- *The conceptual space acts as an intermediate representation between subconceptual knowledge (i.e., knowledge that is not yet conceptually categorized), and symbolically organized knowledge. According to this perspective, the proposed architecture is organized in three computational areas: the subconceptual area; the conceptual area; the linguistic area… These three areas are highly interconnected. There is no privileged direction in the communications among them: some computations are strictly bottom up with data flowing from the subconceptual up to the linguistic area through the conceptual area; other computations combine top-down with bottom-up processing*. (Chella, 1999, p.189)

- *If two words are close enough in meaning that both are reasonable matches for the concept to be described, and yet are not completely identical in meaning, how does the speaker choose the better alternative? Answering this question leads us to issues in the representation of words and concepts, and the relationship between the two. In particular, it leads us to characterize lexical similarity as a lexically based subconceptual distinction. We show in this paper that this view has consequences for schema-based models of conceptual similarity in cognitive psychology.* (Hirst & Edmonds, 2002, p.4)

- *Representing cognitive processes remains one of the great research challenges. Many important application areas, such as clinical diagnosis, operate in an environment of relative magnitudes, counts, shapes, colours, etc. which are not well captured by current representational approaches. This paper presents conceptual spaces as a meso level representation for cognitive systems, between the high level symbolic*

representations and the subconceptual connectionist representations which have dominated AI. (Aisbett & Gibbon, 2001, pp. 189-232)

- *In affective studies there are three emotion dimensions proposed: arousal/activation, valence and dominance. These emotion dimensions estimate the data received from the subconceptual level. At the symbolic level, we are able to express and communicate the meaning 'labeled' at the conceptual level.* (Sugu & Chatterjee, 2012, p.47)

- *What we see now is that there are also senses in which the laws approximately describing cognition at the conceptual level are activation-passing laws like those at the subconceptual level, but operating between units with individual conceptual semantics. Such semantic-level descriptions of mental processing (which include local connectionist models) have been of considerable value in cognitive science*. (Smolensky, 2000, p.558)

- *We experience ourselves as constantly being in direct and immediate epistemic contact with ourselves. What we have in the past simply called a 'self' is not a non-physical individual, but only the content of an ongoing, dynamical process – the process of transparent self-modeling. Any system that, because of its functional architecture, is not able to recognize its self-generated subconceptual representation of itself as a representation, will inevitably fall into a naïve-realistic relationship toward the content of this representation.* (Metzinger, 2000, p.299)

- *Given that we are focusing on the representational aspects of cognitive systems, let us then consider the information on the subconceptual level. How do we distil sensible information from what is received by a set of receptors? Or, in other words, how do we make the transition from the subconceptual to the conceptual and the symbolic levels? These questions point to the representation problems that occur on the subconceptual level.* (Gärdenfors, 1997, p.260)

- *The relation between the symbolic and conceptual levels on the one hand and the connectionist level on the other hand is that connectionism deals with the "fast" behaviour of a dynamic system, while the conceptual and symbolic structures may emerge as "slow" features of such a system. The upshot is that one and the same system, depending on the perspective adopted, can be seen as both an associationist mechanism and as a conceptual space which, in tum, provides a grounding for a symbolic system. Thus, by changing from one perspective to the other, conceptual representations and symbolic inferences can be seen as emerging from dynamic processes in a connectionist system.* (Gärdenfors, 1997, p.268-9)

- *Minds emerge when the activity of small circuits is organized across large networks so as to compose momentary patterns. The patterns represent things and events located outside the brain, either in the body or in the external world, but some patterns also represent the brain's own processing of other patterns. The term* map *applies to all those representational patterns.* (Damasio, 2010, p.18)

- *The combined significance of neuron numbers and organization patterns is the reason why it is not possible to approach the problems of behavior and mind by relying exclusively on the investigation of individual neurons, or of the molecules that act on them, or of the genes involved in the running of their life.* (Damasio, 2010, p.286)

- *Understanding the dynamics of patterns of activity in neural networks and across many networks is undoubtedly essential to understanding how integration and coherence are achieved in brains. For example, there appear to be 'competitions' between networks as the brain settles on a decision whether to fight or flee, and if to flee, whether to run in this direction or that, and so on.* (Churchland, 2002, p.16)

- *Vector coding depends on the idea that features are represented in specific patterns of activity in a population of units, where each neuron has a tuning curve, perhaps quite broad, and tuning curves overlap.… In the struggle to find useful and coherent ways of thinking about how brains represent, the vector/parameter-space turns out to be conceptually powerful… One advantage is that reasonable explanations of a range of behavioral capacities displayed by representing animals emerge quite naturally, without ad hoc miracles. In particular, similarity relations, the be-all of categories and categorical structures, though difficult to address in other theories, gracefully deliver themselves as neighborhood relations in parameter spaces. To put it crudely, the problem of similarity relations need not be solved with hoked-up mechanisms or structures; they are a relatively simple consequence of parameter-space representations.* (Churchland, 2002, p.290; 292)

- *The number of brain structures located between the input and output sectors is quite large. The activity of these 'interposed structures' momentarily constructs and stealthily manipulates the images in our minds. They are the association cortices, the basal ganglia, the thalamus, the limbic system cortices and limbic nuclei, and the brain stem and cerebellum. Together, this 'organ' of information holds both innate and acquired knowledge in the form of 'dispositional representations'…. Dispositional representations exist as potential patterns of neuron activity in small ensembles of neurons…. Innate knowledge is based on dispositional representations in hypothalamus, brain stem, and limbic system. You can conceptualize it as commands about biological regulation. Acquired knowledge is based on dispositional representations in higher-order cortices and throughout many gray-matter nuclei beneath the level of the cortex. The acquisition of new knowledge is achieved by continuous modification of such dispositional representations. When dispositional representations are activated, they can fire other dispositional representations to which they are strongly related…. representations that are not attended to in the clear light of consciousness, but are activated covertly. We know from priming experiments that although these representations are processed*

sub rosa, they can influence the course of the thought process, and even pop into consciousness a bit later. (Damasio, 2006, p.93; 102; 104; 106)

- *We all have direct evidence that whenever we recall a given object, or face, or scene, we do not get an exact reproduction but rather an interpretation, a newly reconstructed version of the original. In addition, as our age and experience changes, versions of the same thing evolve. None of this is compatible with rigid, facsimile representations… memory is essentially reconstructive.* (Damasio, 2006, p.100)

- *My notion of personality is pretty simple: it's that your 'self,' the essence of who you are, reflects patterns of interconnectivity between neurons in your brain… My synaptic theory is an attempt to portray the way the psychological, social, moral, aesthetic, or spiritual self is realized.* (LeDoux, 2002, p.2-3)

- *When someone speaks to you, you decode sentence meaning on the basis of the sound of the words (phonology), the meaning of the words (semantics), the grammatical relations between the words (syntax) and your knowledge about the world (pragmatics). You usually are not aware of performing these operations, but simply do them… Our abilities to perceive the world, attend to objects and events, remember, imagine, and think all operate pretty much in this fashion. Collectively, these processes have been called the psychological or cognitive unconscious.* (LeDoux, 2002, p.11-12)

- *It is now widely recognized that we can have conscious access to the outcome of cognitive processes, but we are not usually aware of the processes that were involved in generating that content.* (LeDoux, 2002, p.23)

- *Although the end result of executive processes (monitoring, resource allocation, task management, conflict resolution, memory retrieval, etc.) was e.g. the representation of your name as conscious content in working memory, it's important to recognize that the executive processes that made this possible functioned unconsciously. As neuroscience pioneer Karl Lashley pointed out in the early 1950s, we are never aware of processing, but only of the consequences of processing. Like the Wizard of Oz, executive processes work behind the scenes.* (LeDoux, 2002, p.191-2)

- *Brain circuits and psychological experiences are not different things, but rather, different ways of describing the same thing… Although single cells have been shown to have remarkable capacities, most researchers accept that ensembles rather than single cells underlie mental and behavioral functions.* (LeDoux, 2002, p.262, 317)

- *Fast, 'automatic' processing does not necessarily imply context-free processing that is immune to goals. The stimulus set, cues from instructions, and task demands can create an environment in which subjects show remarkable sensitivity to dimensions, recurrences, and regularities built into a stimulus set by the experimenter. We are inclined to believe that rather than simply reflecting static knowledge structures and inflexible, automatic 'modules' or stages of processing, unconscious processes demonstrate some of the same flexibility that conscious processes do: they are sensitive to context, compute information along dimensions that fit current tasks, are opportunistic, and are affected by goals.* (Niedenthal, 1994, p.148)

- *The traditional view has been that the cognitive processes carried out within the cortex function hierarchically to control subcortical circuitry related to motivation and emotion. However, research has accumulated indicating that these subcortical circuits often become active well before the cortex. Perhaps more important, multiple projection systems have been discovered that extend from the subcortical regions to the cortex,*

projections that appear to modulate processing within the cortex. Again, models of brain function are beginning to emphasize reciprocal interactions between cognitive processes within the cortex and motivational processes of subcortical areas. (Niedenthal, 1994, p.167)

- *The picture that emerges is one in which specialized computational systems, focused within limbic and paralimbic regions, monitor incoming information in terms of its motivational significance. Upon detecting a significant stimulus, these motivational systems function to regulate the state of the nervous system so as to promote adaptive behavior. This regulation establishes a preparatory pattern of readiness across the motor, autonomic, and endocrine subsystems of the body. At the same time, however, it employs ascending reticular, thalamic, and direct cortical projections to set up a state of readiness across multiple neocortical networks.* (Niedenthal, 1994, p.178)

- *Connectionists may find it necessary to learn how to make networks carry out other processes in addition to pattern recognition (albeit with pattern recognition as an elementary process by which more elaborate processes are carried out). For example, humans do not have to learn each new task de novo. Often they can make use of their knowledge in an analogous domain to help deal with a current domain. Perhaps that knowledge is copied and used as an initial sketch for the new task, so that weights need only be tuned rather than construed from an initially random matrix.* (Bechtel & Abrahamsen, 2002, p.103)

- *Although the simple models of reflex arcs suggest that a single neuron may be sufficient to activate the neuron on which it synapses, in fact a large number of neurons are almost always involved, and the effect of any single neuron on the next is typically quite small. For example, an important feature in the visual system is that input from a specific neuron in the LGN generally makes relatively weak synaptic contacts on a large population of cortical cells rather than a strong synaptic effect on just one or a few neurons.* (Churchland, 1992, p.31)

- *The stress response is mediated through in-concert activity of many brain areas and there is experimental evidence that stress induces structural changes in neuronal networks, in particular in the hippocampus, the prefrontal cortex and the amygdala. Within the hippocampal formation, stress exposure results in remodeling of dendrites of the CA3 pyramidal neurons and in reduced numbers of synapses on these neurons. Furthermore, stress inhibits adult neurogenesis in the dentate gyrus and appears to modulate the GABAergic system. In the prefrontal cortex, repeated exposure to stress causes dendritic retraction and loss of spines in pyramidal neurons whereas in the amygdala stress can elicit dendritic hypertrophy. These microscopically detectable changes in neuronal structures indicate the reorganization of neuronal networks.* (Fuchs, Flugge & Czeh, 2006, p.2746)

- *The microcircuity of the neocortex is bewildering in its anatomical detail, but seen through the filters of physiology, some simple circuits have been suggested. Intensive investigations of the cortical representation of orientation, however, show how difficult it is to achieve any consensus on what the circuits are, how they develop, and how they work. New developments in modeling allied with powerful experimental tools are changing this.* (Kevan, 2002, p.418)

- *In general, from the PDP point of view, the objects referred to in macrostructural models of cognitive processing are seen as approximate descriptions of emergent properties of the microstructure. Sometimes these approximate descriptions may be sufficiently accurate to capture a process or mechanism well enough, but many times they fail to provide sufficiently elegant or tractable accounts that capture the very flexibility and open-endedness of real human cognition.* (Rumelhart & McClelland, 1986, p.12)

- *[The perceptual intelligence of human perceivers also shows] facilitation in the perception of ambiguous letters in unfamiliar letter strings (pronouncable nonwords) which are word-like but not themselves actually familiar… The fact that the word perception model exhibits perceptual facilitation to pronouncable nonwords as well as true words once again illustrates how behavior in accordance with general principles or rules can emerge from the interactions of simple processing elements.* (Rumelhart & McClelland, 1986, p.12)

- *People are good at generalizing newly acquired knowledge. If you learn a new fact about an object, your expectations about other similar objects tend to change… In a network that uses distributed representations, this kind of generalization is automatic. The new knowledge about chimpanzees is incorporated by modifying some of the connection strengths so as to alter the causal effects of the distributed pattern of activity that represents chimpanzees.* (Rumelhart & McClelland, 1986, p.82)

- *The problems of finding a unit to stand for a new concept and wiring it up appropriately do not arise when using distributed representations. All we need to do is to modify the interactions between units so as to create a new stable pattern of activity. If this is done by modifying a large number of connections very slightly, the creation of a new pattern need not disrupt the existing representations. The difficult problem is to choose an appropriate pattern for the new concept.* (Rumelhart & McClelland, 1986, p.86-7)

- *The intuitive idea that larger zones (of activation patterns) lead to sloppier representations is entirely wrong because distributed representations hold information much more efficiently than local ones. Even though each active unit is less specific in its meaning, the combination of active units is far more specific.* (Rumelhart & McClelland, 1986, p.92)

- *We think that PDP models describe the microstructure of the thought process, and the mechanisms whereby these processes come, through practice, to flow more quickly and run together into each other.* (Rumelhart & McClelland, 1986, p.144)