The Psychology of the Placebo Effect: Exploring Meaning from a Functional Account

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Summary

Research on a wide range of medical and non-medical conditions has demonstrated the power of the placebo effect but also calls for the necessity to better understand its psychological mechanisms. The placebo effect appears to be elicited by meaning and expectation. However, expectations have been explored by accounts based on conscious thoughts (i.e., phenomenological approaches). In this paper, a functionally oriented approach (personality systems interaction theory) is introduced which favors the functional properties of mental systems whose operations need not be conscious. It is maintained that only one specific mental system, called extension memory, qualifies to produce the placebo effect since it consists of implicit, parallel-holistic networks integrating (self-)aspects and providing self-regulatory mechanisms. On the basis of this line of reasoning, experimentally testable research ideas are presented.

Key words: functional analysis, placebo effect, PSI theory

The placebo effect allows informative insights into the workings of the human mind because it addresses fundamental issues of the mind-body problem, particularly how mental processes exert an influence on physical states. Whilst contemporary research (re)discovers its interest in the placebo effect, which is reflected in the steady increase in publications, medical interest in this phenomenon is as long-standing as medicine itself. [1] For example, Hippocrates (460–380 B.C.) adopted innocuous and from today's medical point of view futile treatments with great success. Throughout medical history, placebos have deliberately been used on occasion to "cure" ailments and diseases (Kaptchuk, 1998). Along with the advent of the double-blind randomized controlled trial, however, came a decisive shift reducing the use of placebos to controls for efficacy testing of new drugs. Although randomized, controlled trials have become the gold standard in clinical trials, placebo effects frequently appear, compromising to some extent the interpretation of the trial. Attempts to minimize the placebo effect by identifying placebo responders in placebo run-in phases of clinical trials do little to prevent its occurrence (Lee, Walker, Jakul, and Sexton, 2004). As such, placebo effects are often regarded a nuisance, showing up in unpredictable ways, and sometimes to astonishing degrees (Kirsch, Scoboria, and Moore, 2002; Thase, 1999).

Findings from placebo research indicate that placebo effects depend on the *meaning* of the placebo to a patient in a given (treatment) context (Moerman and Jonas, 2002; Walach, 2003). Meta-analyses show that effects substantially increase from meaningless epiphenomena (Hróbjartsson and Gøtzsche, 2001; Kienle and Kiene, 1997) to clinically relevant factors, when their psychological concomitants are investigated (Hull and Bond, 1986; Marlatt and Rohsenow, 1980; Turner, Deyo, Loeser, von Korff, and Fordyce, 1994; Vase, Riley, and Price, 2002; Vase, Robinson, Verne, and Price, 2003; Verne, Robinson, Vase, and Price, 2003). This is reflected in a re-evaluation of a recent meta-analysis (Hróbjartsson and Gøtzsche, 2001) conducted by Vase, Robinson, Verne, and Price (2002), who, opposite to Hróbjartsson and Gøtzsche's approach, not only included clinical trials

where placebos were used as controls for pharmacological effects, but also experimental studies varying participant's knowledge to receive an alleged active agent which in fact is a placebo. The studies varying the informational context produced an effect that was seven times larger than the one obtained by Hróbjartsson and Gøtzsche (for a similar comparison see Vase et al., 2003; Verne et al., 2003). The reason why the practical implications of placebo effects are as yet by and large ignored is, however, at least in part due to the fact that the effects are considered unspecific, difficult to replicate, and hard to predict (Ernst and Resch, 2003; Guess, Kleinman, Kusek, and Engel, 2002; Kirsch, 1997). Such a line of reasoning, however, conceals that active treatment effects, too, are often unpredictable and unspecific. For example, surreptitiously administered analgesics sometimes exert smaller or even no specific effects at all (Benedetti, 1996; Pollo, Vighetti, Rainero, and Benedetti, 2003). Thus, the modern biomedical tradition, which aims at distinguishing specific from non-specific components in treatments, runs the risk of being overly reductionistic.

Evidence for the importance of psychological factors can be derived from neuropsychological findings on placebo effects. For example, placebo analgesia partially depends on the activity of different receptors of the endogenous opioid systems (Petrovic, Kalso, Petersson, and Ingvar, 2002; Petrovic et al., 2005) because the analgesic effect can be inhibited by opioid antagonists (Benedetti et al., 1999; Pollo et al., 2003; Price, 2001). On the other hand, placebo analgesia is not entirely confined to subcortical brain areas. Wager et al. (2004), for example, found that subjective pain involves both direct processes (in pain sensitive neuroanatomical areas via opioid release) and indirect ones (via cognitive appraisal), with the latter occurring after some latency and mostly affecting pain experience. Similar studies on other clinical conditions (Leuchter, Cook, Witte, Morgan, and Abrams, 2002; Lieberman et al., 2004; Mayberg et al., 2002; Zubieta et al., 2005) support the mediating role of the prefrontal cortex in placebo effects. Since the prefrontal cortex represents and maintains evaluative information for control and self-knowledge (Barkley, 1997; Craik et al.,

1999; Fuster, 2000), it exerts a top-down control altering both experience of pain and intensity of pain itself (Wager et al., 2004).

The Psychology of Expectations and the Placebo Effect

Psychological investigations of the placebo effect have identified two major approaches which are not necessarily independent from each other: expectations and conditioned learning. Placebo effects may be acquired through expectations, which, for example, can be brought about by conditioned learning (Ader, 1993; Fillmore, Mulvihill, and Vogel-Sprott, 1994; Fillmore and Vogel-Sprott, 1992; Kirsch and Weixel, 1988; Stewart-Williams, 2004; Wickrameskera, 1980). On the other hand, (conscious) expectations do not necessarily bear on previous learning episodes and thus can be generated in a given context (Hull and Bond, 1986; Mikalsen, Bertelsen, and Flaten, 2001). Yet, one important prerequisite for the placebo effect to show is that the expected effect is meaningful to the patient (Amanzio, Pollo, Maggi, and Benedetti, 2001; Kirsch, 1999; Moerman et al., 2002; Pollo et al., 2003).

Traditional ways to operationalize expectations in placebo research – in analogy to psychological research – are based on introspective accounts (i.e., consciously accessible thoughts). Such approaches have at least two shortcomings: (1) they tend to overrate conscious processes (e.g., conscious expectations) as the primary source of behavioral change, and (2) they posit that symbolic representations alone are the primary prerequisite for behavioral change. These limitations have been amply demonstrated by research showing that the human brain implicitly and parallel-holistically processes a great deal of information (Beeman and Bowden, 2000; Beeman, Friedman, Perez, Diamond, and Lindsay, 1994; Bowers, Regehr, Balthazard, and Parker, 1990; McClelland and Rumelhart, 1995; Rumelhart and McClelland, 1986). This form of processing simultaneously integrates almost unlimited information at speeds that are much greater than can be handled by conscious (e.g.,

sequential, analytical) processing. Due to this characteristic, implicit processing is not (fully) conscious and can only be partially explicated. Likewise, implicit processing affects equally emotions, motivation, self-regulation, and other forms of human functioning and (self-)knowledge (Craik et al., 1999; Nadel and Moscovitch, 1997; Rotenberg and Weinberg, 1999; Wheeler, Stuss, and Tulving, 1997). What follows from that is a biased and limited explanation of expectations and other possibly important psychological factors, such as self-regulation, when introspective methods alone are used (e.g., via self-reports). This has important implications for placebo research: when beliefs and expectations are assessed in order to explore their functional significance for the placebo effect, self-report and introspection may not fully assess implicit mechanisms. However, mechanisms may have far more relevance to the size and nature of the placebo effect. Unfortunately, placebo effects have as yet been investigated merely in terms of consciously accessible thought contents, for example, by asking participants what they experienced or expected when taking the unknowingly inert substance. A number of conclusive findings suggest that the identification of underlying mechanisms, that is, conscious or unconscious psychological functions, may be more important. Using a functional approach, which attempts to uncover subsystems describable in terms of classes of functions, could answer a number of inconsistencies found in placebo research. Among these are, for instance, questions why sometimes placebo mediated treatment success can be superseded by differential effects (Leuchter et al., 2002), why verbal instructions alone may elicit the placebo effect (Flaten, 1998), but sometimes do not (Walach, Schmidt, Dirhold, and Nosch, 2002), why the placebo effect may be elicited without direct learning history (Kirsch, 2002), why expectations about adverse effects may be accompanied by compensatory (counter-regulatory) concomitants (Fillmore and Blackburn, 2002), or why the placebo effect may show in different outcome parameters to varying degrees (Schneider et al., 2006).

Accounting for the Dynamics of Functions: Personality-Systems-Interaction Theory

In the past decade, a comprehensive functional approach has been developed which can be used to investigate placebo effects, within the framework of personality-systems-interaction (PSI) theory by Kuhl (2000, 2001). Personality-systems-interaction theory accounts for several functional levels of varied complexity (i.e., from low-level functioning associated with affect to higher-order functioning of self-regulation) and describes their dynamic interplay by spelling out conditions under which these systems interact. The theory comprises six systems of which two are high-level, two are low-level, and two are modulatory (affective) subsystems. Two systems and one subsystem are associated with experience and two (plus one) with behavior. The systems may be regarded as complex personality aggregates characterized by distinct functional properties. The two experiential systems generating expectations, and therefore associated with the placebo effect, are *extension memory* and *object recognition*. [2] Extension memory is conceptualized as high inferential (complex) and object recognition is regarded as low inferential (elementary). Their activational characteristics are antagonistic, that is, activation of extension memory decreases the activation of object recognition and vice versa. Extension memory derives its denomination from the neuronal fabric of the right prefrontal cortex which consists of extended associative networks (Beeman et al., 2000; Bowden and Beeman, 1998; Scheibel et al., 1985). These allow for a simultaneous, sub-symbolic computation of a vast number of constraints and multiple inputs from both cognitive and affective subsystems through parallel-processing. Extension memory is a central executive system which simultaneously integrates countless amounts of information. Extension memory also forms the basis for implicit self-representations (autonoetic knowledge), that is, integrated representations of internal states, needs, emotions, somatic feelings, or autobiographical experiences (Keenan, Nelson, O'Connor, and Pascual-Leone, 2001; McClelland, Koestner, and Weinberger, 1989; Nyberg, Cabeza, and Tulving, 1996; Wheeler et al., 1997). Moreover, functions of extension memory

also encompass attention processes which monitor inner and outer ambience (vigilance) and enhance those perceptual contents which match actual relevant and implicit networks of needs, expectations, and other self-structures. Due to this characteristic, processes of extension memory are not fully conscious. One of the typical functions of extension memory is down-regulation of negative affect elicited by aversive, threatening or unpredictable experiences because extension memory is tightly linked with vegetative and somatosensory processes (Fuster, 2000; Garavan, Ross, and Stein, 1999; Kapur et al., 1995; Rotenberg, 2004).

In contrast, object recognition serves to recognize objects. The term “object” denotes a percept which can be abstracted (discerned) from its background due to specific discrepancy mediating features, for example, concrete things, singular aspects, feeling, sensation etc. Specifically, the system enhances those objects deviating from expectations and self-aspects activated in extension memory. Object recognition separates singular sensory modalities and abstracts them from specific contexts. It is closely linked with one of the cornerstones of cortical pathways (the so-called vision-for-perception stream) where information generated in the primary visual cortex projects into the inferior temporal cortex and further in the prefrontal cortex (Ungerleider and Mishkin, 1982; for a summary see Koch, 2004). However, the functional characteristics of object recognition are not limited to these neurological pathways but encompass a number of additional features. As a primarily perceptual system, object recognition focuses on explicit identification and recognition of elementary sensations (e.g., a visual object, an emotion, or semantic category). Characteristic for object recognition (especially in connection with negative affect) is a focus on discrepancies and on sensations that diverge from previously held expectations, wishes and the like. Contrary to the functional properties of extension memory, object recognition allows for an explicit, conscious registration of sensory impressions, which encompasses a relatively rigid analytical

categorization (yes/no, black/white, etc.). The following table summarizes the functional properties of the two experiential systems.

Personality-systems-interaction theory decomposes global attention processes regarding the function of each system and the input to be amplified. Whilst extension memory amplifies congruence-sensitive information, object recognition enhances incongruence-specific information. Due to the parallel distributed structure of extension memory, those signals are amplified that are rare, fragmented and/or ambivalent, and that can be represented as an extended network of acceptable possibilities (and not, as in the case of object recognition, as an unambiguous, clear-cut object). The functions of extension memory and object recognition are antagonistic, that is, extension memory-based attention processes amplify everything that (even remotely) resembles the criterion, and that is coherent in that sense, whereas attention processes based on object recognition only amplify information that reflects a clear cut criterion (e.g., the exact literal meaning of a word or an exactly defined goal state).

From the mutually antagonistic relationship between object recognition and extension memory follows that the activational strength of either system alters the way expectations about the placebo effect affect bodily and mental processes. For example, PSI theory distinguishes different modes of functioning; facilitatory and inhibitory ones. The facilitatory systems coalition is denoted as self-regulation and is mainly implicit and effortless in nature. In this mode, largely implicit processes integrate various subsystems and processes. Typical self-regulatory functions are emotion regulation, attention regulation, arousal regulation, and motivation regulation. Here, negative affect is down-regulated due to the activation of the extension memory. The inhibitory mode, called preoccupation describes a systems configuration where object recognition “dominates” with negative affect being high. Here, self-access is inhibited because negative affect cannot be down-regulated (through the activation of the extension memory). As a consequence, consciousness is focused on one

isolated aspect (often causing uncontrollable rumination) because object recognition is especially active. The different modes of functioning are also expressed in two types of personality: action orientation and state orientation. Action-oriented individuals mainly access the facilitatory mode of self-regulation under stressful circumstances (i.e., uncertainty, or anxiety). On the other hand, in the absence of stress, for instance, when negative affect induced by failure or uncertainty is not present, action-oriented individuals cannot effectively dispose of their self-regulatory resources. For state-oriented individuals, the reverse is true. They perform better than their action-oriented counterparts in non-threatening situations, but less well when exposed to stressful situations. Thus, differences in modes of functioning are primarily to be expected as personality-situation interactions (Diefendorff, Hall, Lord, and Strean, 2000; Kazén, Baumann, and Kuhl, 2003; Koole, Kuhl, Jostmann, and Vohs, 2004; Kuhl and Beckmann, 1994).

Expectation, Meaning, and the Placebo Effect

According to personality systems interaction (PSI) theory, the central functional differences between extension memory and object recognition outlined above can be assumed to be constitutive for placebo mediated expectations and the physiological and mental reactions associated with them. Depending on where the expectation is generated, different consequences will ensue. Under the premise that the placebo effect is brought about by the meaning of the placebo and its context (Moerman and Jonas, 2002), only those expectations should elicit a placebo effect that are represented in extension memory, that is, in a semantic network of remote associations and coherent complexes of symbolic meaning. Symbols in extension memory evolve from combining experiential and knowledge fragments to a sensible whole, which cannot be fully explicated. [3] This notion is supported, for instance, by therapeutic knowledge that compliance is more decisive for therapy success than the question whether verum or placebo is administered (Coronary Drug Project Research Group, 1980).

According to PSI theory, compliance should be greater the more self-aspects are integrated in extension memory, which, as a consequence, increases (subjective) meaning. According to another, equally important functional property, only expectations generated in extension memory should be accompanied by a placebo effect because extension memory is closely linked with self-regulatory mechanisms affecting a variety of cognitive and somatosensory processes (Baumann and Kuhl, 2002; Bolte, Goschke, and Kuhl, 2003; Fuhrmann and Kuhl, 1998; Kazén et al., 2003; Koole and Jostmann, 2004).

Indirect Empirical Support for the Functional Significance of Extension Memory

As yet, there is no direct evidence available to validate the assumptions outlined above. However, there are a number of indirect recent findings pointing to the tenability of the theoretical implications derived from PSI theory.

1. In the study on treatment of depression by Leuchter et al. (2002) the verum and placebo groups showed comparable treatment outcomes, although they differed with regard to the activation of brain areas involved. Patients responding to placebo administration were found to have enhanced metabolic rates in areas where PSI theory locates the functional properties of extension memory (right hemisphere, prefrontal). On the other hand, patients who responded to the antidepressant medication showed a metabolic decrease in these areas. If replicated, this result would indicate that active treatment impairs self-regulative (i.e., self-healing) efficiency whilst placebo treatment fosters it.

2. Mayberg et al. (2002) showed the same remission rate of symptoms in patients from both the antidepressant and the placebo group, but metabolism of brain areas increased only for the verum group in subcortical areas (brain stem, hippocampus), whereas both groups displayed comparable activation of the prefrontal cortex and the limbic system. The fact that both left and right hemispheric areas were involved in the placebo effect

is interesting inasmuch as PSI theory attributes to the left prefrontal hemisphere functions associated with self-control (i.e., impulse control), which are adaptive when activated in alignment with self-regulation.

3. A pain relieving placebo effect in two fMRI study by Wager et al. (2004) was found in participants who were treated with an analgesic cream (placebo) after receiving strong aversive electric shocks (study 1) or thermal stimuli (study 2). A placebo effect only showed when strong aversive pain was applied (study 1), that is when the meaning of pain was high and, consequently, its reduction relevant. Furthermore, expectation of pain relief was associated with increased neural activity in prefrontal cortex areas both during and in anticipation of pain (study 2).

4. Turner, Jensen, Warms, and Cardenas (2002) found conscious thought contents not to be directly associated with the placebo effect. When comparing the effects of active treatment of chronic pain after spinal cord injury versus active placebo (similar side effects) there was a correlation of conscious expectation and therapy success only in the verum group, although both groups showed similar effects.

5. In a study on irritable bowl syndrome, Lieberman et al. (2004) found a strikingly direct confirmation of the suggested functional mechanisms of the modulation of the placebo effect. Symptom improvement after placebo administration was solely mediated by the right ventrolateral prefrontal cortex, which exerted an inhibitory impact on brain structures modulating pain experience (dorsal anterior cingulate). The authors explain this effect by a pathway similar to the one outlined in PSI theory.

6. A recent PET study by Zubieta et al. (2005) investigating sustained and individually preset pain intensity for a prolonged period of time found placebo administration (intravenously applied physiological saline) to be associated with an increase in the average rate of algesic stimulus required to maintain pain. While increased activation of endogenous μ-opioid neurotransmission in the placebo condition occurred in

several associative, higher-order brain regions and was correlated with various psychological aspects of pain (e.g., pain intensity, pain unpleasantness, negative mood), this relationship was not found for the left dorsal prefrontal cortex. Instead, the activity of the latter was negatively associated with the expected analgesic effect rated before placebo administration.

7. In a PET study on painful osteoarthritis (Pariente, White, Frackowiak, and Lewith, 2005) real acupuncture and placebo acupuncture (i.e., a needle which does not penetrate the skin but gives the appearance to do so) did not differ with regard to cerebral activation. Expectation and belief regarding the beneficial treatments was modulated by the right dorsolateral prefrontal cortex, the right anterior cingulate and the midbrain.

Experimental Research Suggestions

On the basis of the psychological architecture and mechanisms described by PSI theory, there are different ways to experimentally test the assumption of extension memory dependence and the placebo effect. If proven valid, PSI theory enables a better understanding of the underlying psychological mechanisms of the placebo effect, the boundary conditions under which its occurrence is maximized, and the ways it may be more reliably deployed both in therapeutic practice and in clinical efficacy testing.

Extended versus restricted meaning. According to the functional properties of extension memory and object recognition, the representation format of the expectation is critical in eliciting the placebo effect. Put differently, only expectations generated in extension memory, according to the line of reasoning presented here, are sufficient to produce it. On the other hand, expectations generated in object recognition should not foster a placebo effect because they lack extended networks and connectedness with somatosensory functioning.

Expectations represented in extension memory are linked to relevant (meaningful) self-aspects, or entail a network of remote associations requiring (implicit) attention processes (i.e., rare or unexpected effects). There is evidence suggesting that remote associations indeed are an important prerequisite to elicit a placebo effect when experimental instructions encompass a continuum of possible (Dinnerstein and Halm, 1970; Luparello, Leist, and Lourie, 1970; Lyerly, Krugman, and Clyde, 1964) or unusual and even opposite effects (Fillmore et al., 1994). In the Dinnerstein and Halm (1979) and Lyerly et al. (1964) experiments, expectancies of likely reactions (e.g., "lowered mood, calmer, more relaxed") were used to increase the effect. On the other hand, in the Fillmore et al. study participants led to expect alcohol-induced impairment performed better than those expecting enhancement, because they unconsciously counter-regulated alcohol-induced impairment. Experimentally, the two experiential PSI systems, extension memory and object recognition, can be activated by varying the instructions such that either a range of possible physiological and psychological responses may be expected (e.g., "You will experience becoming either more alert, more joyful, more aroused, or more energetic") or one concrete aspect of the response is separated (e.g., "You will experience being more alert"). It is predicted that providing a range of possible responses will activate extension memory which produces expectations accompanied by psychological and physiological changes under placebo administration.

Content-independent activation of extension memory. Rather than relying on verbal reports on experiences upon placebo intake, involvement of extension memory is testable in a content-free manner. If corroborated, this would indicate that subsymbolic mechanisms are associated with the placebo effect, relativizing the explanatory power of self-reported expectations to predict the effect. As outlined above, the make-up of extension memory consists of remote associations of implicit (self-)knowledge that cannot fully be verbalized due to its parallel-holistic nature. Working on the assumption that activation of the extension

memory is a sufficient condition, content-free activation of extension memory should suffice to produce the placebo effect. Direct hemispheric stimulation to activate extension memory avoids verbal reporting and introspection as limiting factors. One way to test this assumption may be derived from an operationalization within the so called self-infiltration paradigm (Baumann, Kuhl, and Kazén, 2005). Self-infiltration is regarded as a direct measure of integrated self-representations provided by extension memory. To assess self-infiltration (as indexed by a tendency toward false self-ascription of assigned tasks), Baumann et al. employed a nonreactive method that allowed experimentally varying the objective self-other status of a goal (see also Baumann and Kuhl, 2003; Baumann et al., 2005; Kuhl and Kazén, 1994). Participants performed unilateral muscle contractions of each hand to activate the counterlateral hemisphere (Schiff, Guirguis, Kenwood, and Herman, 1998) and influence self-infiltration. Self-infiltration was observed after right-hand muscle contractions (left-hemispheric activation) and was absent after left-handed muscle contractions (right-hemispheric activation).

An experimental set-up within the placebo paradigm would comprise contiguously activating the extension memory, for example, by squeezing a soft ball with the counterlateral hand, upon intake of placebo. As in the study by Baumann et al., where left-handed ball squeezing facilitated access to extension memory and its autonoetic networks (e.g., feelings, self-aspects) and enhanced accuracy of judgments on preferences and right-hand squeezing produced deteriorations respectively, it is predicted that the placebo effect is associated with left-handed squeezing, whilst it is smaller or absent with right-handed squeezing. Activation of extension memory should thus accompany a much stronger placebo effect, as indicated, for example, by higher correlations with verbal instructions.

Coherence dependent activation of the placebo effect. Another way to experimentally activate extension memory is to present participants with tasks requiring detection of semantic

coherences. The ability to intuitively perceive coherences in word material (Beeman et al., 1994; Bowers et al., 1990) depends on the activation of extended networks of meaning and holistic representations and can therefore directly be used to test the placebo effect if the latter is described as enhancing such performance. Since implicit coherence perception may depend on current mood states (Baumann and Kuhl, 2002; Bolte et al., 2003), instructions about mood enhancing effects of a placebo may additionally increase coherence perception. When using substances whose pharmacologic effects are well known, this experimental set-up additionally offers yet another important tool to investigating the psychological mechanisms of the placebo effect. For example, caffeine mainly enhances cognitive attentional processes and perceptual processing by preventing performance with simple tasks (Lorist and Topsa, 2003; Ruijter, Lorist, Snel, and Ruiter, 2000). Therefore, in the placebo caffeine paradigm (see e.g., Schneider et al., 2006), implicit coherence performance would be more enhanced after intake of placebo if individuals expect caffeine to improve coherence perception.

Affective change and down-regulation of negative affect. Due to the disordinal relationship between self-regulation related personality types (action vs. state orientation) and affective situation, the extension memory dependency of the placebo effect can be operationalized by exposing participants to negative affect inducing conditions. This would be done after instruction about expected placebo effects but before placebo is taken. Action-oriented individuals have been shown to effectively down-regulate negative affect, for instance, induced by performance pressure (Koole and Jostmann, 2004), negative word stimuli (Baumann and Kuhl, 2002, 2003), or enactment of difficult intentions (Fuhrmann and Kuhl, 1998). Under such conditions, a smaller placebo effect should be found for state-oriented individuals who have only limited access to extension memory needed to down-regulate negative affect. Down-regulation of negative affect has been shown to operate on the level of unintentional, fast, flexible, and efficient processes of which the individual is not

aware but which is nonetheless informed by highly affirmed self-aspects. Overly focusing on negative affect generating sources narrows attention to singular (discrepant) aspects and impedes access to the extended networks provided by extension memory which are deemed necessary for the placebo effect to appear.

Placebo effect and self-regulatory mechanisms. Provided that access to extension memory is crucial for the placebo effect, correlations with self-regulatory mechanisms can be expected (e.g., affect regulation). This assumption is derived from the neuropsychological findings (see above) indicating that high-inferential brain systems (i.e., the prefrontal cortex) both mediate experience and exert influence on hierarchically lower areas (e.g., generating pain). Therefore, the placebo effect should be predictable by self-regulatory mechanisms, which, according to PSI theory, are exerted effortlessly and implicitly. In contrast, pharmacological effects should show much fewer associations with self-regulatory mechanisms, because they are not mediated by self-relevant (i.e., meaningful) expectations or, if they are, this effect occurs to a much lesser extent. Whenever extension memory is experimentally activated (e.g., by one of the techniques described above) one would thus expect to find substantial correlations of the placebo effect with implicit self-regulatory indices. One way to explore the self-regulation hypothesis is to employ the volitional components inventory constructed on the basis of PSI theory (Fuhrmann and Kuhl, 1998). It assesses more than thirty functional mechanisms related to different PSI systems and assesses the ability to access different modes of functioning with more flexibility, when situational constraints (e.g., obstacles, challenges, frustration) are encountered. Should the present hypothetical association between the placebo effect and self-regulation hold, important insights into the underlying psychological mechanisms of the placebo effect could be gained.

Outlook

Greater understanding of the ways placebo effects occur will support developing more consistent, low risk interventions with greater therapeutic benefit for patients with various conditions. Likewise, this knowledge may be gainfully used in efficacy testing of active treatments. Applying PSI theory to placebo research allows manifold ways to test the functional significance of different psychological systems and mechanisms. On the basis of PSI architecture, I contend that the representational format of the placebo-related expectation is the key variable that decides upon the placebo effect. According to the basic idea brought forward in this paper, only expectations represented in a largely implicit network of multiple (self-)aspects, and connected with inferential knowledge and self-regulatory competencies have the capacity to bring about the placebo effect. In contrast, expectations limited to a single (isolated), and in that sense less meaningful, aspect would qualify to a much lesser extent. If replicated, the herein purported involvement of extension memory in the placebo effect has direct consequences both for pharmaceutical efficacy testing and therapeutical effectiveness. Once knowledge about the underlying mechanism is available, pharmacological testing procedures can no longer afford to discard placebo treatment as an inactive control for active treatments. On the other hand, medical and psychotherapeutic practitioners may more reliably incorporate placebos to the benefit of their patients without running the risk of detrimental side effects often seen with active pharmacological treatment.

Involvement of the self portion of extension memory brings about meaning and compliance with treatment regardless of the pharmacological agent or active treatment. This may be the reason why placebo treatment (i.e., treatment without specific therapeutic components) yields effects no different from established psychotherapies if they are structurally equivalent, for example regarding number and duration of treatment, format etc (Baskin, Tierney, Minami, and Wampold, 2003). Spelling out the conditions necessary for the placebo effect to occur also affords the means to enhance the power of the placebo. For example, placebo effects in analgesia could be amplified upon identification of underlying

self-regulatory (self-healing) mechanisms associated with it. Likewise, treatment with placebo can be rendered more meaningful by activating a broad range of coherent self-(aspects).

Unfortunately, involvement of extension memory can only be implemented via an indirect route because knowledge of the placebo treatment or dampened expectations (by double-blinding in pharmacological testing, for example) deteriorates the placebo effect. In therapeutic practice, it is often served by external modulation - the therapist, or the medical context being used to access the benefit of self-healing until the patient's resources are sufficiently restored and can be self-initiated. Interestingly, findings from placebo research suggest that meaningful expectations alone may suffice to unleash these powers. The more this meaning is extended, that is, represented and integrated in a network of vastly implicit (self-)knowledge operating in a mode of parallel distributed processing, the larger and more enduring the beneficial workings of the placebo effect should be.

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End notes

[1] The word “placebo” derives from an incorrect translation of the ninth verse of Psalm 116 in the Old Testament (Lasagna, 1986). The original Hebrew text contained the word eth-al-ech translating to “I shall *walk* [with the Lord in the land of the living].” However, in the Greek translation the word euarestaso was used from which the Latin translation placebo derives translating to “I shall please.”

[2] For the sake of simplicity, the two behavioral systems are not discussed here because they are not directly associated with expectations. Analogous to the two experiential systems, extension memory and object recognition, intention memory and intuitive behavior control are antagonistic with the first being high-inferential and the latter being elementary.

[3] The primary mode of perception associated with functions of extension memory is best described as feeling rather than explicating.