Chapter 4

Unspecific Effects of Caffeine Consumption: When Does the Mind Overrule the Body?

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Abstract

Although much is known about the pharmacokinetics of caffeine (i.e., what the body does to the drug), its pharmacodynamics (i.e., what the drug does to the body) are less well understood. Specifically, the psychological effects associated with caffeine intake may often run counter to what might be expected pharmacologically. Being one of the most consumed stimulants worldwide the instrumental value of caffeine covers a broad range of partially opposing ends. For example, the effect (caffeinated) coffee exerts on human functioning depends to a great deal on the expectation of the consumer. People drink coffee to get started in morning, to enhance performance, or even to unwind after straining experiences. Likewise, the instrumental value of coffee consumption may be bound to psychosocial factors, such as enhancing group coherence. Also, coffee may be consumed for diet-related health issues to prevent diseases like diabetes, cancer, heart diseases, or gastrointestinal problems.

In this chapter, an overview of placebo studies is given to demonstrate the importance of psychological factors. Specifically, results from the so called placebo caffeine paradigm will be discussed to show that the study of the placebo caffeine effect lends itself to a better understanding of the psychological factors involved with caffeine effects. Several ways to methodologically disentangle pharmacologic and psychological effects will be introduced. From this, it will be concluded that the widely employed way of testing drug effects (the Randomized Control Trial) is insufficient to fully understand

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the health effect of caffeine since it is aimed at minimizing psychological factors enhancing the effect (e.g., learning effects, expectation, context). It will be shown that the health effects of caffeine are brought about by synergistically intertwined specific and non-specific factors, which, in real-life situations, always work together and make up the totality of effects. Finally, a functionally oriented psychological theory will be introduced helping to explore the psychological mechanisms associated with unspecific effects.

1. Introduction

Caffeine has a long history of use. Its consumption dates back to early mankind and has taken many forms. In tea, it has been savored in Asia for almost 5,000 years, in coffee humans have consumed it for some 1,000 years. Over the last hundred years, cola drinks, ready-to-drink tea and coffee beverages have steadily gained in popularity. Today, coffee is the second most consumed beverage in the world next to water. The fact that caffeine is the most widely consumed behaviorally active substance in the world has made it subject to vigorous scientific investigation. The biochemical mechanisms underlying the actions of caffeine are well understood. If consumed in doses habitually consumed by humans, caffeine primarily blocks adenosine A_1 and A_{2A} receptors, causing a parallel increase in motor activity and decrease in the expression of genes throughout brain regions like the caudate-putamen and nucleus accumbens (Fredholm, Bättig, Holmén, Nehlig, and Zvartau, 1999; Svenningsson, Nomikos, Ongini, and Fredholm, 1997). Unlike other stimulants (e.g., cocaine), caffeine does not significantly increase the release of dopamine or activate the D_1 neurotransmission in the nucleus accumbens. Rather, it increases transmission through cells equipped with dopamine D_2 receptors in this nucleus and throughout the basal ganglia. Since the effect is inhibitory in nature, the overall activity of this brain region is much less affected by caffeine. Its effects are biphasic with low doses being stimulant and pleasant and high doses being aversive and disturbing. This U-shaped dose-response determines whether caffeine can act as reinforcing agent and thus enhance beneficial effects on subjects.

The behavioral effects of caffeine cover a broad range of phenomena like increased subjective alertness, improved reaction time, and enhanced encoding of novel information. For example, in a series of related studies on central nervous effects (Ruijter, De Ruiter, Snel, and Lorist, 2000; Ruijter, Lorist, and Snel, 1999; Ruijter, Lorist, and Snel, 2000; Ruijter, Lorist, Snel, and Ruiter, 2000) caffeine was found to have increasing properties on arousal sustaining attention and attenuating vigilance decrements. This was evidenced by increased amplitudes of different ERPs (event related potentials) in EEG recordings in fatigued participants, showing for example in the frontal P2 and the parietal P3 component. Caffeine displays its effect in the brain in the working memory and higher level control and co-coordinating functions (prefrontal cortex) as well as heightened information processing (parietal cortex). However, although caffeine is supposed to have a general arousing effect due to the binding of adenosine to its receptor sites resulting in an increase in the levels of other neurotransmitters (e.g., acetylcholine, noradrenaline, dopamine, and serotonin), information processing is more pronouncedly affected under conditions in which availability of energetical resources is insufficient (e.g. tiredness or boredom). Moreover, beneficial effects on tasks involving cognitive performance appear to be mainly expected for tasks of

little complexity showing predominantly in the output stage of the information processing (Lorist and Topsa, 2003).

Despite the still growing body of knowledge about the effects of caffeine on, for instance, peripheral physiology (cardiovascular system), sleep, mood, arousal, and pain, the pattern of results is far from being homogeneous. In fact, many findings somewhat contradict the fundamental aspects of psychopharmacology with regard to motor, psychomotor, and cognitive performance. Evidently, there appears to be a dissociation between the pharmacokinetics of caffeine (i.e., what the body does to the drug) and its pharmacodynamics (i.e., what the drug does to the body). This instigated a debate arising in the mid 1990s by James (1994) who contended that studies conducted over several decades contained one fundamental methodological flaw by merely including placebo controls without heeding participants' habitual caffeine intake. According to this line of reasoning, abstinence prior to study participation could result in withdrawal symptoms like headache, sleepiness, or lack of concentration. Hence, the performance and mood effect of caffeine would not reflect a real net gain but rather a restoration of decrements to normal levels of functioning. Therefore, the beneficial effects seen in caffeine would simply be counter-regulating detrimental withdrawal symptoms. In fact, there is empirical evidence for the tenability of this claim (James, 1998; James and Gregg, 2004; James, Gregg, Kane, and Harte, 2005; Phillips-Bute and Lane, 1998; Rogers, Martin, Smith, Heatherley, and Smit, 2003; Yeomans, Ripley, Davies, Rusted, and Rogers, 2002). Interestingly, according to the withdrawal hypothesis, caffeine actually has a detrimental effect on mood quality and cognitive performance.

There are, however, empirical findings which cannot be fully reconciled with the withdrawal effect. For example, Smit and Rogers (2000) demonstrated psychostimulant properties after overnight caffeine abstinence with surprisingly small doses (12.5 mg) for both high and low caffeine consumers. Quite counter-intuitively, the effects found in this study failed to increase as a function of the doses administered, i.e. a dose eight times higher did not show significant increments. In a study including multiple doses of caffeine, regular coffee consumers who were fatigued by carrying out a prolonged testing schedule reported more positive mood and improved performance on a number of different tasks (Smith, Sutherland, and Christopher, 2005). In a series of double-blind, randomized, controlled experiments investigating the role of hidden versus open administration of caffeine in regular coffee consumers involving a caffeine abstinence period of at least 12 hours, very large effects were found for caffeine consumption compared to control groups in primarily cardiovascular measures (Schneider et al., 2006; Schneider and Walach, in preparation). Moreover, in one experiment employing the use of decaffeinated coffee (Experiment 1, Schneider et al., 2006), participants believing to have consumed a strong cup of coffee reported elevated alertness. Post-hoc analyses showed that this effect was not attributable to caffeine cravings or differences in withdrawal symptoms associated with fasting and caffeine abstinence.

Obviously, the impact caffeine has on human health and performance is multifaceted. It is clear from the heterogeneity of the findings that the effects may dissociate significantly depending on the method used. Besides specific effects like drug dose, sample compositions, or drinking habits, so called unspecific effects have thus far been widely neglected. Unspecific effects refer to the fact that their underlying mechanisms are as yet unknown

(Schneider, 2007). Unlike other beverages predominantly serving a more fundamental satisfaction of basic biological needs (e.g., water), consumption of caffeine, for instance in the form of coffee, serves many different purposes. These are psychological and psychosocial in nature and thus bound to cognitions (e.g., expectations) and learning experience. For example, an athlete ingesting caffeine prior to working out will ascribe a totally different instrumental value to a cup of coffee than a business manager who socializes with a partner during a meeting. Since large epidemiological studies support the notion that caffeine may have beneficial effects on health, for example as a protective agent in high-risk individuals with liver diseases (American Gastroenterological Association, 2005), caffeine may be assumed to be increasingly consumed for dietary and health care reasons.

In the following, I will outline a fundamental fallacy associated with the thinking that drug effects can unambiguously be reduced to specific effects to understand their modes of action. It will be shown that this mindset is deeply rooted in the belief that placebo administration in experiments is an exclusive way to control for unwanted effects (artifacts) not otherwise regarded meaningful in explaining the drug effect.

2. Placebo Caffeine Effects

The use of placebos in clinical trials dates back to the introduction of the *Randomized Controlled Trial* (RCT) in 1948 (British Medical Journal, 1998). Since then it has become the gold standard and cornerstone of pharmacologic efficacy testing (Biller-Andorno, 2004). The logic behind using placebos is that a pharmacological agent should show its superiority to a "sugar pill" exempt from any specific contents. Administration of placebos grounds on the reasoning that any effects emerging are artificial and therefore neglectable. Such confounds encompass the regression to the mean, the natural course of a disease, or spontaneous fluctuations (Kienle and Kiene, 1997). Clinical testing practice, however, shows that placebo responses may considerably compromise the interpretation of trials. Despite the notorious lack of published negative results (which is referred to as the file drawer problem), reviews of existing data bases, for example from the US pharmacologic industry on depression, show a remarkably high rate of non-superiority of pharmacologic agents over placebo (Kirsch, Scoboria, and Moore, 2002; Thase, 1999). Attempts to minimize placebo effects, for instance by identifying placebo responders in placebo run-in phases of clinical trials, largely fail (Lee, Walker, Jakul, and Sexton, 2004). Because placebo effects are to a great deal difficult to replicate, and hence hard to predict, they are considered unspecific. However, active treatment effects, too, are at times unpredictable and unspecific. For example, surreptitiously administered analgesics sometimes exert smaller or even no specific effects at all (Pollo, Vighetti, Rainero, and Benedetti, 2003). From this it may be concluded that the modern biomedical tradition risks being too overly reductionistic by merely focusing on specific treatment components.

There has been much controversy on the real nature of placebo effects. While there have been overly enthusiastic claims on the powerfulness of placebo effects (Beecher, 1955), in part justified methodological critique has at times been too undifferentiated regarding the conditions which are placebo-responsive and those which are not (Hróbjartsson and

Gøtzsche, 2004). There is a growing body of evidence substantiating the therapeutic relevance of placebo effects across a wide range of phenomena (Sauro and Greenberg, 2005; Stolk, ten Berg, Hemels, and Einarson, 2003; ter Riet, de Craen, de Boer, and Kessels, 1998; Turner, Deyo, Loeser, von Korff, and Fordyce, 1994; Vase, Riley, and Price, 2002; Vase, Robinson, Verne, and Price, 2003; Vase, Robinson, and Price, 2005).

Nonetheless, there also has been much confusion. One central misunderstanding regarding placebo effects revolves around definitional clarity. For example, obviously factually wrong definitions attribute to placebos a causative mechanism (cf. Moerman and Jonas, 2002). Fortunately, recent definitions have proven more fruitful. One proposition suggests to regard placebo effects as psychosocial context effects arising from treatment or therapy (Benedetti, 2006). Another related definition points to the meaning of an intervention to which an individual responds (Moerman and Jonas, 2002). These definitions have the advantage to be positive, semiotic, and theory-independent. However, as will be shown later, they do not spell out the psychological mechanisms necessary for placebo effects to show. I will therefore suggest a new definition heeding functional properties.

Much from what has been learned about placebo effects stems from *experimental* placebo research. In a nutshell, experimental placebo designs vary conditions such that the probability of the occurrence of the effect is maximized. Unlike in RCTs where subjective probability for placebo administration is set at .5, participants in experimental placebo research are made to believe to receive an active agent when actually given a placebo. From the many models available, the placebo caffeine paradigm particularly lends itself to study placebo effects mainly due to two reasons. First, the effects can be studied in healthy individuals, and second, people share a common cultural stereotype about how coffee operates and what effects are to be expected. There are a number of findings supporting the usefulness of the placebo caffeine paradigm. For example, Kirsch and Weixel (1988) showed that a deceptive administration of placebo caffeine (i.e. decaffeinated coffee) produced an increase on pulse rate, systolic blood pressure, and subjective mood. The magnitude of this effect was paralleled by participants' confidence that they had in fact consumed caffeine. On the other hand, double-blind administration of decaffeinated coffee produced placebo responses which were approximate mirror images of those found for deceptive placebo administration. Studies varying the expectation about caffeine effects found that positive (enhancing) expectations predicted the placebo effect even when no active agent was administered. Participants who were not instructed, and thus did not have any particular belief about the beverage, did not display any change in psychomotor performance (Fillmore and Vogel-Sprott, 1992; Fillmore, Mulvihill, and Vogel-Sprott, 1994). In a study disentangling expectancy and pharmacologic effects by providing different types of information on the content of the beverages (caffeinated and decaffeinated coffee), different responses were found for different measures. Whilst pharmacologic factors primarily influenced participants' physiology (blood pressure), expectancy about the drug primarily affected self-reported mood and assessment of performance (Fillmore and Blumenthal, 1992). The modulating effects of expectancy were also demonstrated in a study by Fillmore, Roach, and Rice (2002). Alcohol drinkers who expected an antagonist effect of caffeine showed greater impairment in a pursuit rotor task from alcohol than those expecting no such effect. More importantly, expectancy effects were independent of whether caffeine of placebo

caffeine was administered. This finding is interesting inasmuch as little or no actual antagonist effect of caffeine can be expected on alcohol-induced impairment. In a recent study by Anderson & Horne (in press), sleepy participants were given a cup of decaffeinated coffee and verbally primed to suggest caffeinated coffee. Results showed significantly fewer lapses and shorter reaction times compared to a control group. These results are interesting inasmuch as they relativize the withdrawal effect of caffeine mentioned earlier. Specifically, the alleged restoration of decrements to normal levels of functioning is not dependend on caffeine, but can be elicited by means of suggestion.

It should be noted, however, that placebo effects show in different measures to varying degrees and establishing the most sensitive indicators is challenging. For example, two studies failed to demonstrate placebo caffeine effects (Walach, Schmidt, Bihr, and Wiesch, 2001; Walach, Schmidt, Dirhold, and Nosch, 2002). While the reproduction of placebo effects is dependent on many as yet not fully understood boundary conditions (Schneider, 2007), the Walach et al. studies most probably failed due to an insufficient induction of a strong expectation and/or the use of rather insensitive measurements. For example, a series of studies investigating caffeine-associated stimuli and information, administering caffeine or placebo in either orange juice or coffee, caffeine-associated stimuli (taste, smell) increased physiological arousal (Flaten and Blumenthal, 1999; Mikalsen, Bertelsen, and Flaten, 2001). Information about the content of the beverage also modulated arousal in the direction indicated by the information. In two recent experiments disentangling pharmacologic from psychological effects by investigating social stereotypes of decaffeinated coffee (smell and taste), no modulating effect on pharmacologic effects could be found (Schneider et al., 2006a). Rather, stimuli-associated stimuli showed to be an important prerequisite for the placebo effect to show (i.e., decaffeinated coffee produced a placebo effect). This pattern of result was paralleled by two subsequently conducted experiments only administering orange juice which was either caffeinated or not (Schneider et al., in preparation). Yet, despite large pharmacologic effects, misinformed information about the alleged content of the beverage did not suffice to produce placebo effects.

3. Mechanisms of the Placebo Caffeine Effect

Traditionally, two approaches have been put forward to explain placebo effects. According to the mentalistic theory, individuals' cognitions like expectations, meaning, needs, or wishes determine the effect (Kirsch, 1999). According to the conditioning theory, placebo effects are the result of learning processes, i.e. the pairing of unconditioned and conditioned stimuli (Ader, 1993; Wickrameskera, 1980). Figure 1 displays the learning model for placebo caffeine affects. They can be regarded the consequence of the pairing of the unconditioned stimulus [UCS] caffeine with the conditioned stimuli [CS] taste and smell. Hence, the unconditioned reaction [UCR] arousal is elicited by the CS making arousal a conditioned reaction [CR].
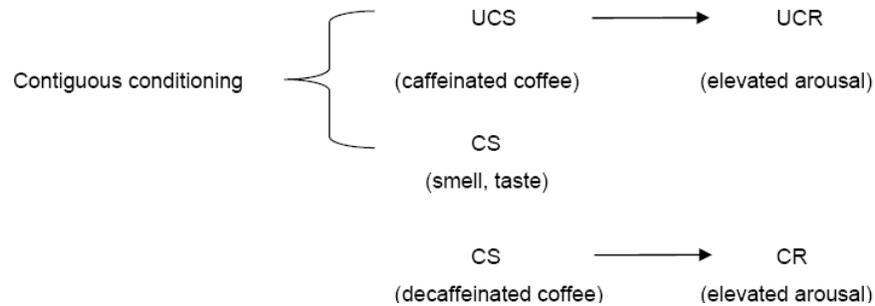
Figure 1. The caffeine placebo effect as a result of conditioned learning.

It should be noted that both approaches are not necessarily mutually exclusive. In fact, they are often synergistic. Unfortunately, unlike other placebo effect phenomena, the neurobiological mechanisms of the caffeine placebo effect have not yet been subjected to investigation. Placebo analgesia, for example, has been found to be maximal when expectation and conditioning are combined (Amanzio and Benedetti, 1999; Colloca and Benedetti, 2006). Yet, expectancy effects have shown to be associated with a different neurological pathway than conditioning effects: Placebo analgesic effects bearing on expectation can be blocked with the opioid antagonist naloxone. Placebo effects brought about by a conditioned treatment (i.e. the injection) with a non-steroid anti-inflammatory drug (ketorolac), have a different pathway because they can't be inhibited. Furthermore, a number of several studies have demonstrated that placebo effects involve different brain areas than pharmacologic effects. These involve subcortical processes (e.g., in pain sensitive neuroanatomical areas via opioid release) and cortical ones (via cognitive appraisal), with the latter occurring after some latency and mostly affecting pain experience (Wager, et. al, 2004; Wager, 2005). Similar findings on the mediating role of the prefrontal cortex in placebo effects have been reported on a broad range of symptoms like depression, irritable bowl syndrome, or chronic pain (cf. Pacheco-Lopez, Engler, Niemi, and Schedlowski, 2006; Schneider, 2007) Consequently, when expectations are engaged, the prefrontal cortex, which maintains evaluative information for control and self-knowledge (Craik et al., 1999; Fuster, 2000), exerts a top-down control modulating experience and physiological processes. It is important to note that expectations need not necessarily be conscious in order to exert a placebo effect (Turner, Jensen, Warms, and Cardenas, 2002). As shown above, from the many effects observed for caffeine ingestion, it may be assumed that in addition to the specific (pharmacologic) effects of caffeine, unspecific (psychological) mechanisms exert an influential role over and above specific ones. This requires a somewhat different methodological approach to fully understand the impact of caffeine on health.

4. Methodological Approaches

Several suggestions have been proposed to study the placebo effect. Benedetti (2006) suggested to surreptitiously administer the pharmacologic agent in order to exempt the treatment form the unspecific effects elicited by the psychosocial context. In so doing, the

proportion of the placebo effect can be determined when open and hidden administrations are compared. Although this is a straightforward methodology, it may be questioned whether its ecological validity is sound. For example, to determine bio-availability, absorption rate and pharmacodynamics of caffeine, hidden administration of the agent is likely to have different effects than oral ingestion. Therefore, to study the effects of caffeine under real life conditions this experimental paradigm is not viable.

Another way of studying pharmacologic and psychological factors of caffeine consumption is suggested by the so called balanced placebo design (Marlatt and Rohsenow, 1980). It combines the usual placebo design with an "antiplacebo" design resulting in a 2(drug, placebo) x 2(expectation, no expectation) arrangement. By administering placebo and drug under conditions in which the participants expect to receive an inert substance, independent effects of psychological and pharmacologic effects can be parceled out. As can be seen in Figure 2 (dotted line), a "true" pharmacologic effect would be obtained in an experimental condition were participants are given caffeine but are told to have received placebo.

Information

		Caffeine	Placebo	None
Substance	Caffeine	Pharmacological effect + Placebo response	Pharmacological effect	
	Placebo	Placebo response	Confounds	
	None	--	--	Control

Figure 2. The extended balanced placebo design; Placebo effect: Placebo response minus control.

Likewise, when placebo is given but participants are told they ingested caffeine, placebo responses are discernable. It is, however, important to note that the balanced placebo design is only able to unravel placebo *responses* but not placebo *effects*. This is because placebo responses comprise both placebo effects and confounds like artifacts, spontaneous remission, regression effects and the like (Ernst and Resch, 2003; Kirsch and Sapirstein, 1999). Hence, to determine placebo effects the balanced placebo design must be "extended" by including a zero control group with which placebo responses are compared (solid line).

The balanced placebo design has been primarily used in alcohol research with expectancy effects comparable to drug effects (for an overview see Marlatt and Rohsenow, 1980). Since then, it has only seldom been fully employed and somewhat fell into oblivion (for a few exceptions, cf. Juliano and Brandon, 2002; Perkins et al., 2004; Perkins et al., 2008). In placebo caffeine research, this is partly due to the fact that placebo response effects showed as main effects having subsequent researchers focus on comparisons of placebo and control group.

Research on the effects of caffeine on health would benefit greatly from employing the extended balanced placebo design to study the relationship between specific and unspecific effects. However, to understand unspecific effects from a psychological point of view, it may not suffice to primarily focus on conscious thought contents in determining expectations or

meaning. This is because people only have limited access to mental processes and cannot fully or adequately explicate (verbalize) them. This is suggested by neurobiological findings showing implicit and parallel-holistic processes of the brain (Beeman, Friedman, Perez, Diamond, and Lindsay, 1994; Beeman and Bowden, 2000; Bowden and Beeman, 1998; Bowers, Regehr, Balthazard, and Parker, 1990; Rumelhart and McClelland, 1986) and that these processes also comprise functional properties like self-regulation, motivation, or affect (Craik et al., 1999; Keenan, Nelson, O'Connor, and Pascual-Leone, 2001; Nadel and Moscovitch, 1997; Quirin, Kazén, Rohrmann, and Kuhl, in press; Quirin, Koole, Baumann, Kazén, and Kuhl, 2007; Rotenberg and Weinberg, 1999; Wheeler, Stuss, and Tulving, 1997). Thus, in placebo research, simply asking people about their cognitions may not suffice when meaning and expectations are assessed. Yet, functional approaches, uncovering subsystems describable in terms of classes of functions, have not been employed in placebo research. In the following, a functionally oriented theory is introduced according to which psychologically important subsystems can be evaluated for their significance of placebo effects.

5. Dynamics of Psychological Functions: Personality-Systems-Interaction Theory

Within the framework of Personality-Systems-Interaction (PSI) Theory a comprehensive functional approach has been developed which lends itself to studying placebo effects (Kuhl, 2000; Kuhl, 2001). The theory comprises two high-level and two low-level systems. These 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. The two behavioral systems are not directly implicated in placebo effects. They are called intention memory and intuitive behavior control with the first being high-inferential and the latter being elementary (see Figure 3). For the sake of simplicity, they will not be further discussed here.

Extension memory is high inferential (complex) and object recognition is low inferential (elementary). Their activational characteristics are antagonistic, that is, activation of extension memory decreases the activation of object recognition and vice versa. This is depicted by the change of colors in the arrows connecting the antagonist systems. Extension memory derives its denomination from the neuronal fabric of the right prefrontal cortex which consists of extended associative networks (Scheibel et al., 1985; Bowden and Beeman, 1998). 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 almost unlimited amounts of information. Extension memory also forms the basis for implicit self-representations (so called autonoetic knowledge), that is, integrated representations of internal states, needs, emotions, somatic feelings, or autobiographical experiences (Keenan et al., 2001; McClelland, Koestner, and Weinberger, 1989; Nyberg,

Cabeza, and Tulving, 1996; Wheeler et al., 1997). Moreover, functions of extension memory also encompass attention processes (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 (Borod and Madigan, 2000; Garavan, Ross, and Stein, 1999; Kapur et al., 1995; Rotenberg, 2004). This is shown as self-relaxation in Figure 3.

Left Hemisphere   **Right Hemisphere**

Intention Memory

Planning
Logical, sequential processing
Goal-oriented behavior

Thinking

Extension Memory

Contextual self-knowledge
Generation of meaning and
"extended" expectations

Feeling

Self-relaxation   **Self-motivation**

Object Recognition

Perception of discrepancies/
negative states
Generation of "restricted" expectations

Sensation

Behavior Control

Rudimentary/learned behavior programs
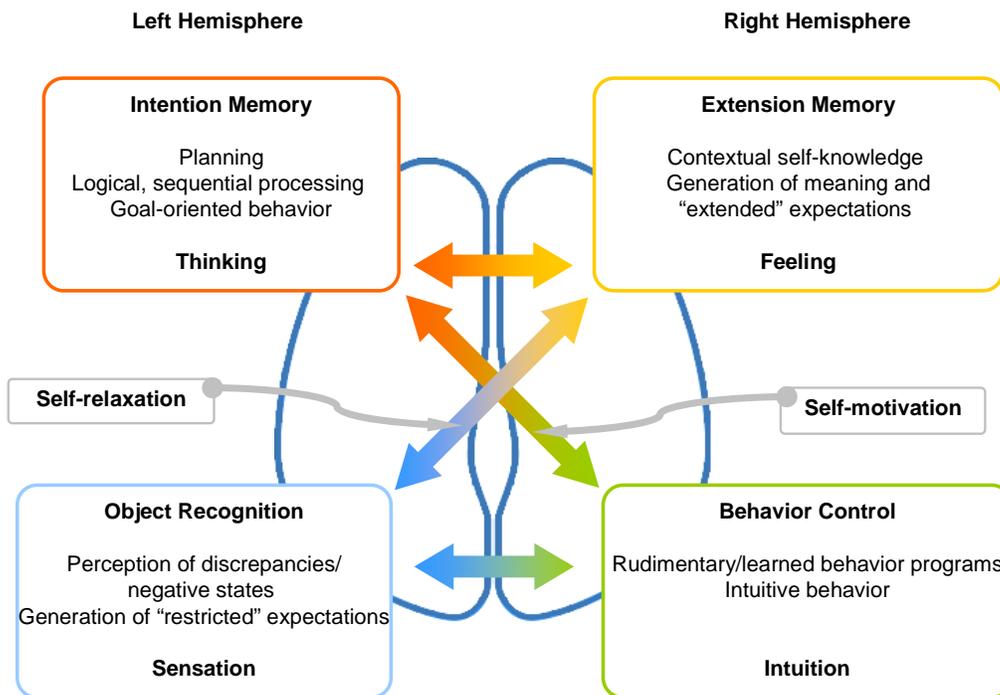Intuitive behavior

Intuition

Figure 3. Personality-System-Interaction Theory (PSI).

In contrast, object recognition serves to recognize percepts which can be abstracted (discerned) from their background by specific discrepancy mediating features, for example, concrete things, singular aspects, feelings, sensations etc. Specifically, the system enhances those objects deviating from expectations and self-aspects activated in extension memory. Object recognition 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). 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 (i.e., black/white).

6. The Placebo Effect Revisited: Expectation, Meaning, and Their Functional Significance

According to personality systems interaction (PSI) theory, functional properties determine the powerfulness of placebo-associated expectations and meaning. In other words, different responses follow depending on whether the expectation is generated in extension memory or in the object recognition system. As noted above, strong placebo effects have been found when the meaning of the placebo (treatment) was personally relevant to the participants. This is especially the case for highly aversive states like pain (Zubieta, Yau, Scott, and Stohler, 2006), but basically also holds for placebo caffeine effects (or similar drug effects for that matter). Put differently, only those context factors elicit a placebo effect that are generated and represented in a semantic network of remote associations and coherent complexes of symbolic meaning (extension memory). Furthermore, 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. In contrast, expectations generated in the object recognition system would not suffice to produce significant placebo effects because they lack the connectedness to relevant (meaningful) self-aspects and the network of remote associations requiring (implicit) attention processes (i.e., rare or unexpected effects). Remote associations indeed may be an important prerequisite to elicit placebo effects. For example, Dinnerstein and Halm (1970) and Lyerly, Krugman, and Clyde (1964) found expectancy effects only for experimental conditions where drug effects were introduced as a continuum of possible reactions. Furthermore, as noted above, a number of studies support the notion that placebo effects incorporate self-regulatory mechanisms of the prefrontal cortex which cannot be found for drug effects. This would indicate that active treatment impairs self-regulation whilst placebo treatment fosters it. This implication is supported by leading neuroscientists who recently called for a systematic investigation of self-regulatory factors to psychologically better understand placebo effects (Benedetti, Mayberg, Wager, Stohler, and Zubieta, 2006). Given that placebo caffeine research also found bodily and mental changes when no caffeine was administered, the effects found for caffeinated substances at least in part may bear on such underlying mechanisms. This would explain the somewhat opposing effects found for caffeine: whether a strong cup of coffee exerts an effect on, for instance, cognitive performance, would be mediated by the psychosocial context in which it is consumed and the expectation and meaning which are associated with it. Clearly, the relationship between caffeine and placebo caffeine effects may assume different forms. For example, the psychological mechanisms may supersede or counter-regulate the pharmacologic effects (Fillmore and Blachburne, 2002; Schneider et al., 2006), be neglectable when no expectations are associated with the caffeinated beverage (James, 1998)

or be additive when specific and unspecific effects are stressed (Flaten and Blumenthal, 1999).

One corollary derived from PSI Theory is that subsymbolic mechanisms are associated with the placebo effect because expectations and cognitions involved are not fully conscious. Bearing on the findings from hemispheric activation stimulation to activate extension memory (Baumann, Kuhl, and Kazén, 2005) contiguously activating the extension memory, for example, by squeezing a soft ball with the counterlateral hand, upon intake of placebo should ensue much stronger placebo effects. Likewise, since extension memory affords complex cognitive processes, for example the detection of semantic coherences (Baumann and Kuhl, 2002; Bolte, Goschke, and Kuhl, 2003), placebo caffeine effects would comprise coherence perception whilst caffeine effects, which primarily affect relatively simple cognitive processes (Lorist and Topsa, 2003; Ruijter et al., 2000), would not. Hence, when studying (placebo) caffeine effects implicit coherence performance would be enhanced in individuals expecting caffeine to improve coherence perception. Furthermore, if the activation of extension memory is constitutive for the placebo effect, there should be correlations with self-regulatory mechanisms (e.g., affect regulation). This, in turn, would make placebo effects predictable by self-regulatory mechanisms, which, according to PSI theory, are exerted effortlessly and implicitly. Such a relationship should not hold for pharmacological effects because they are, to a much lesser degree, mediated by psychological mechanisms (i.e. self-relevant expectations).

Following this line of reasoning, I suggest the following definition for placebo effects including functional psychological boundary conditions.

Placebo effects are unspecific intervention effects depending on the individual's implicit competency to construe meaning in the psychosocial context, and to respond to this meaning by means of self-regulation.

Conclusion

The effects caffeine exerts on health cannot be reduced to pharmacological pathways but comprise psychological mechanisms also. The findings on placebo caffeine effects suggest that so called unspecific effects substantially contribute to caffeine effects. The mind in fact may overrule the body when specific expectations with a certain meaning are held. Whether psychological factors exert a significant influence over and above pharmacologic effects is determined by the context in which caffeine is ingested. Disentangling the mediating role of self-regulatory factors in caffeine effects may benefit the understanding of when and how health effects may be expected. To do so, traditional ways of testing caffeine (e.g., employing RCTs) should be complemented with those which allow testing of caffeine and placebo under different conditions (extended balanced placebo design). To better understand psychological factors, functional approaches and methods should be employed (e.g., PSI theory and the diagnostic tools derived from it). Although from a pragmatic point of view a separation of specific and unspecific effects is not necessary (in most cases even disadvantageous),

understanding the underlying mechanisms and boundary conditions of the context is important in determining health-related caffeine effects.

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