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Mind does really matter: Evidence from neuroimaging studies of emotional self-regulation, psychotherapy, and placebo effect

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Abstract

This article reviews neuroimaging studies of conscious and voluntary regulation of various emotional states (sexual arousal, sadness, negative emotion). The results of these studies show that metacognition and cognitive recontextualization selectively alters the way the brain processes and reacts to emotional stimuli. Neuroimaging studies of the effect of psychotherapy in patients suffering from diverse forms of psychopathology (obsessive-compulsive disorder, panic disorder, unipolar major depressive disorder, social phobia, spider phobia, borderline personality) are also examined. The results of these studies indicate that the mental functions and processes involved in diverse forms of psychotherapy exert a significant influence on brain activity. Neuroimaging investigations of the placebo effect in healthy individuals (placebo analgesia, psychostimulant expectation) and patients with Parkinson's disease or unipolar major depressive disorder are also reviewed. The results of these investigations demonstrate that beliefs and expectations can markedly modulate neurophysiological and neurochemical activity in brain regions involved in perception, movement, pain, and various aspects of emotion processing. Collectively, the findings of the neuroimaging studies reviewed here strongly support the view that the subjective nature and the intentional content (what they are ''about'' from a first-person perspective) of mental processes (e.g., thoughts, feelings, beliefs, volition) significantly influence the various levels of brain functioning (e.g., molecular, cellular, neural circuit) and brain plasticity. Furthermore, these findings indicate that mentalistic variables have to be seriously taken into account to reach a correct understanding of the neural bases of behavior in humans. An attempt is made to interpret the results of these neuroimaging studies with a new theoretical framework called the Psychoneural Translation Hypothesis.

Keywords: Emotional-self-regulation; Psychotherapy; Placebo effect; Brain; Mind; Neuroimaging; fMRI; PET; SPECT; Psychoneural Translation Hypothesis

Contents

Abbreviations: fMRI, functional magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography; BA, Brodmann area; PFC, prefrontal cortex; LPFC, lateral prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; MPFC, medial prefrontal cortex; IAPS, International Affective Picture System; BOLD, blood oxygenation level dependent; MOFC, medial orbitofrontal cortex; OCD, obsessive-compulsive disorder; CBT, cognitive-behavioral therapy; MDD, major depressive disorder; IPT, interpersonal psychotherapy; SSRI, selective serotonin reuptake inhibitor; rCBF, regional cerebral blood flow; DLPFC, dorsolateral prefrontal cortex; PD, Parkinson's disease; STN, subthalamic nucleus; rACC, rostral anterior cingulate cortex; IBS, irritable bowel syndrome; dACC, dorsal anterior cingulate cortex; LOFC, lateral orbitofrontal cortex; PTH, Psychoneural Translation Hypothesis

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1. Introduction: aims and scope of the review

During the last decade, there have been a growing number of neuroimaging studies (functional magnetic resonance imaging [fMRI], positron emission tomography [PET], single photon emission computed tomography [SPECT]) of emotional self-regulation, psychotherapy, and placebo effect. This review article is concerned with these neuroimaging studies. The main goal of this article is to demonstrate that the results of these studies strongly support the view that the subjective nature and the intentional content (what they are ''about'' from a first-person perspective) of mental processes (e.g., thoughts, feelings, beliefs, volition) significantly influence the functioning and plasticity of the brain. In other words, mentalistic variables have to be seriously taken into account to reach a correct understanding of the neuropsychological bases of behavior in humans. Confusion concerning the relative importance of neurophysiological and mentalistic variables can lead to important misunderstandings about causes and effects in the study of human behavior (Schwartz et al., 2005).

Such a mentalistic view is supported by the fact the explanatory and predictive value of agentic factors like beliefs, goals, aspirations, desires, and expectations is very high (Bandura, 2001). This mentalistic outlook stands against psychophysical identity theory for which mind, intentionality, and consciousness can be left out to explain human behavior (Lewis, 1994). This view also opposes epiphenomenalism. For this stance, mental processes and subjective experience are merely an epiphenomenal picturing of underlying neuronal processes (Fuchs, 2002). It is noteworthy that the psychophysical identity theory and epiphenomenalism are still espoused by a number of contemporary neuroscientists interested in the so-called mind-brain problem.

Neuroimaging studies of conscious and voluntary regulation of various emotional states (sexual arousal, sadness, negative emotion) are reviewed in the second section of this article. In the third section, we present the neuroimaging studies measuring the effect of psychotherapy in patients suffering from diverse forms of psychopathology (obsessive-compulsive disorder, panic disorder, unipolar major depressive disorder, social phobia, spider phobia, borderline personality). Neuroimaging studies of the placebo effect in healthy individuals (placebo analgesia, psychostimulant expectation) and patients with Parkinson's disease or unipolar major depressive disorder are examined in the fourth section. In the fifth section of this review article, we discuss the implications of these neuroimaging studies regarding the relationships between subjective experience, mental processes, neurophysiological processes and human behavior.

2. Neuroimaging studies of emotional self-regulation

2.1. Definition of emotional self-regulation

According to evolutionary psychology, emotions represent biologically based modes of adaptation to changing environmental demands (Levenson, 1994; Tooby and Cosmides, 1990). Evolutionary psychology further claims that emotions have emerged in the course of evolution on account of their capacity to adequately coordinate the various response systems (e.g., cognitive, subjective or experiential, physiological, and behavioral) that characterize emotion's multicomponential nature. In so doing, emotions have helped the human species to face challenging events and survive (Levenson, 1994). Emotions, however, are not always the most appropriate response to the various situations encountered in daily life.

Indeed, despite the many possible benefits of emotion, deleterious situations may occur when one is blindly following emotional impulses. Moreover, negative emotions represent one of the main causes of suffering and dysfunction on our planet. This is why it is paramount for humans to learn how to properly control and modulate their emotional reactions using their cognitive capacities.

Emotional self-regulation refers to the set of cognitive processes by which emotions are self-regulated, i.e., the ways individuals influence which emotions they have, when they have them, and how they experience and express these emotions (Gross, 1999). This form of self-regulation implicates changes in one or more of the various components (or response systems) of emotion (Gross, 1999). These changes involve modifications in what Thompson (1990) has called ''emotion dynamics'', i.e., the magnitude, rise time, duration, and offset of responses in the various components of emotion (Gross, 1999). Generating, maintaining, decreasing, or increasing either positive or negative emotional responses represent the various expressions of emotional self-regulation (Cole et al., 1994; Langston, 1994; Masters, 1991; Parrott, 1993). This ability implicates several types of adjustments favoring the adaptation to life circumstances (Cole et al., 1994). The cognitive strategies used to self-regulate emotion can be more or less conscious, effortful, and controlled (Gross, 1999). These cognitive strategies are numerous and include, among others, rationalization, reappraisal, and suppression (Gross, 1999).

Emotional self-regulation constitutes one of the cornerstones of socialization and moral development (Kochanska et al., 1997). Consistent with this, there is mounting evidence that impulsive aggression and violence arise as a consequence of defective regulation of anger (Davidson et al., 2000). Furthermore, several lines of evidence indicate that a chronic inability to self-regulate negative emotions, such as sadness and fear, may play a pivotal role in the genesis of clinical depression and anxiety disorders (Davidson et al., 2000; Jackson et al., 2000). Because the ability to self-regulate negative emotion is essential to a healthy psyche, therapists teach their clients how to use efficient emotional self-regulatory strategies in several modern psychotherapeutic approaches.

Since the cognitive processes underlying emotional self-regulation are closely meshed with those implicated in emotion generation, it has been theorized that emotional self-regulation is an integral part of emotion (Frijda, 1986). With respect to the relationship between emotion regulation and generation, Gross (2001) has proposed that emotion may be regulated at five different points in the emotion-generative process: (1) selection of the situation, (2) modification of the situation, (3) deployment of attention, (4) change of cognitions, and (5) modulation of experiential, behavioral, or physiological responses. In Gross's terminology, the first four of these cognitive processes are antecedent-focused while the fifth is response-focused.

2.2. Sexual arousal

In the first neuroimaging study of emotional self-regulation (Beauregard et al., 2001), blocked-design fMRI was used to identify the neural substrates of conscious and voluntary regulation of sexual arousal, a positive emotional state. Ten healthy male volunteers were scanned during two experimental conditions, i.e., a sexual arousal condition and a suppression condition. In the sexual arousal condition, volunteers viewed series of erotic film excerpts. They were instructed to react normally to these stimuli, i.e., they had to allow themselves to become sexually aroused during the viewing of the erotic film excerpts. In the suppression condition, volunteers were instructed to suppress any feelings elicited by the erotic film excerpts. In order to do so, volunteers were requested to become a detached observer of the erotic film excerpts and the sexual arousal induced by these stimuli. Such a metacognitive strategy shares some similarity with mindfulness, a central mental state in Buddhist forms of meditation (Nyanaponika, 2000). To assess the emotional reactions of the volunteers to the film excerpts, at the outset of each condition, they were asked to rate verbally – on a numerical (analogue) rating scale – the intensity of primary emotions felt during the viewing of both categories of film excerpts.

Phenomenologically, the viewing of the erotic film excerpts during both experimental conditions induced a state of sexual arousal in all volunteers. In the suppression condition, most volunteers reported having been successful at distancing themselves from the sexual arousal induced by the erotic film excerpts. Consistent with this, the mean level of sexual arousal was significantly higher in the sexual arousal condition than in the suppression condition. In line with the results of a previous study (Karama et al., 2002), the viewing of the erotic film excerpts, in the sexual arousal condition, produced a significant activation of the right amygdala, right anterior temporal pole (Brodmann area [BA] 38), and hypothalamus. The suppression condition was associated with activation peaks in BA 10 of the right lateral prefrontal cortex (LPFC) and BA 32 of the right rostral-ventral anterior cingulate cortex (ACC). Interestingly, no significant loci of activation were noted in the amygdala, anterior temporal pole, and hypothalamus (Fig. 1). These results provide strong evidence for the view previously proposed that emotional self-regulation depends on a neural circuit in which prefrontal cortical areas mediate the cognitive modulation of emotional responses generated at a subcortical level (Davidson et al., 2000; Nauta, 1971; Tucker et al., 1995). Moreover, these results are consistent with findings indicating that the LPFC is involved in metacognitive/executive top-down processes, which refer to the ability to monitor and control the information processing necessary to produce voluntary action (Flavell, 1979). This prefrontal cortical region has been implicated in the selection and control of behavioral strategies and action (Fuster, 1999), especially in the inhibition of inherent response tendency (Damasio, 1995; Frith and Dolan, 1996; Fuster, 1997; Goldman-Rakic, 1987). These results also concur with the view that, by virtue of its anatomic connections with brain regions implicated in the modulation of autonomic and endocrine functions, such as the amygdala, hypothalamus, and orbitofrontal cortex (OFC), the rostral-ventral subdivision of the ACC plays a key role in the regulation of the autonomic aspect of emotional responses (Bush and Posner, 2000;

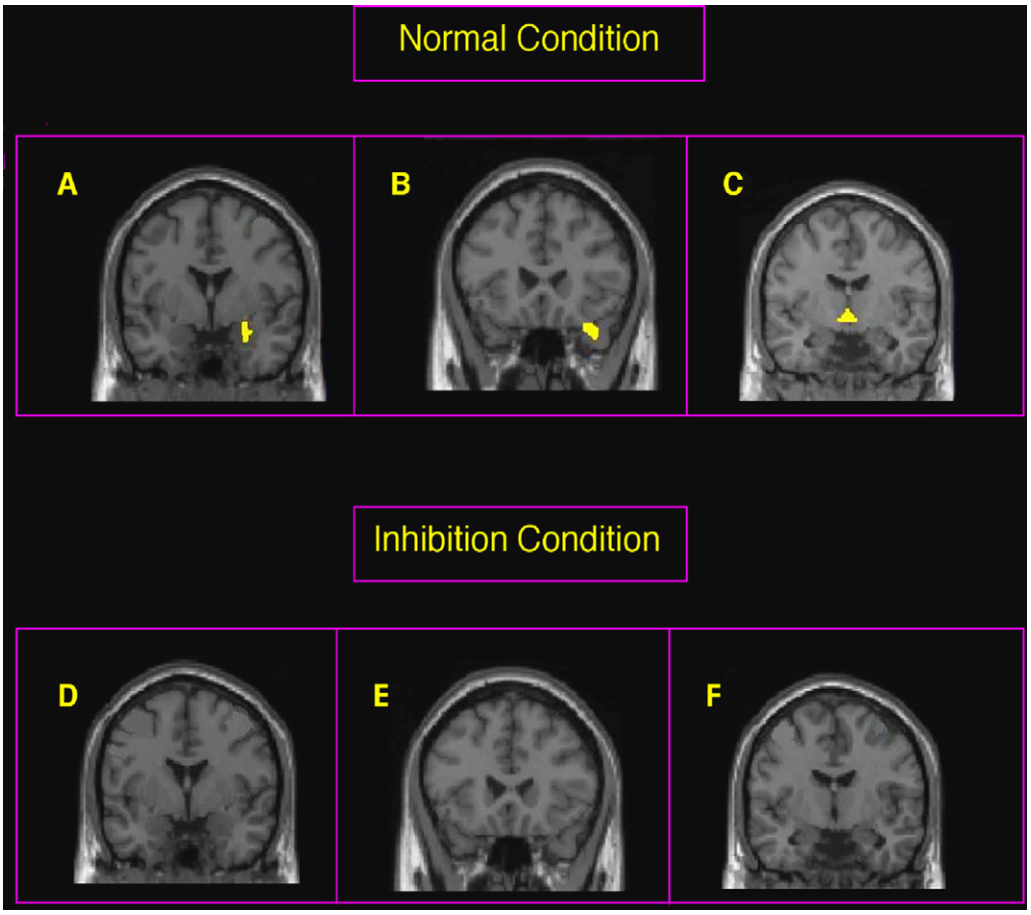

Fig. 1. Statistical activation maps showing limbic – paralimbic structures defined *a priori*. In the sexual arousal condition, greater activation during the viewing of erotic film excerpts relative to the viewing of emotionally neutral film excerpts was noted in the right amygdala (A), right anterior temporal pole (B), and the hypothalamus (C). In the suppression condition, no significant loci of activation were seen in the amygdalae (D), the anterior temporal polar region (E), and the hypothalamus (F) (reproduced with permission of the Society for Neuroscience from Beauregard et al., 2001).

Devinsky et al., 1995; Vogt et al., 1992). The fact that this portion of ACC has both afferent and efferent connections with neural structures mediating autonomic functions, such as the periacqueductal gray, the dorsal motor nucleus of the vagus, and preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord (for a review, see Benes, 1997), is supportive of such a view.

2.3. Sadness in adults

A protocol similar to that used in the Beauregard et al. (2001) study was utilized in another fMRI study (Lévesque et al., 2003), this time to investigate the neural correlates of conscious and voluntary regulation of sadness, a primary emotion with a negative valence (Plutchik, 1994). Twenty healthy female volunteers were scanned during a sad condition and a suppression condition. Phenomenologically the mean level of reported sadness was significantly higher in the sad condition than in the suppression condition. Neurally, significant bilateral loci of activation were measured, during the sad condition, in the anterior temporal pole (BA 21 and BA 38) and the midbrain. Significant loci of activations were also seen in the right ventrolateral prefrontal cortex (VLPFC) (BA 47), left amygdala, and left insula. In the suppression condition, significant loci of activation were noted in the right OFC (BA 11) and right LPFC (BA 9). Additionally, positive correlations betweeen self-report ratings of sadness and blood oxygenation level dependent (BOLD) signal increases were noted in the right OFC (BA 11) and right LPFC (BA 9).

In the suppression condition, the right LPFC activation demonstrated that, in addition to being involved in the voluntary down-regulation of a positive emotional state such as sexual arousal (Beauregard et al., 2001), this prefrontal cortical region is also associated with the voluntary down-regulation of a negative emotion such as sadness. These results are consistent with a variety of evidence indicating that the LPFC plays a crucial role in willed actions (Frith and Dolan, 1996) and with the holding in mind of information on which an action is to be based (Fuster, 1999; Goldman-Rakic, 1987; Roberts and Wallis, 2000). Robust activation of the right OFC (BA 11) was also noted during down-regulation of sad feelings. From a neural systemic point of view, this prefrontal region is located at the junction of the prefrontal associative cortex and the limbic system. Given the fact that the OFC sends projections to the amygdala, diencephalon, brain stem and spinal cord, this prefrontal region has been associated with the

integration of visceral-autonomic processes with cognitive and behavioral processes (Eslinger, 1999a; Ongür et al., 1998; Rempel-Clower and Barbas, 1998). It has been further proposed that the OFC plays a central role in the adaptation to complex changing environments (Eslinger, 1999b) and the regulation of socio-emotional behavior in settings involving social affiliation and social judgment, self-awareness, inhibition, and the self-guidance of behavior through judgments and decisions about one's actions (Bechara et al., 1994; Cummings, 1993; Damasio, 1995; Damasio et al., 1990; Dolan, 1999; Elliott, 1990; Eslinger, 1999b; Fuster, 1997; Giancola and Zeichner, 1994; Grafman et al., 1996; Grafman and Litvan, 1999; Lapierre et al., 1995; Mesulam, 1986; Zald and Kim, 1996). The OFC is the only PFC region richly connected to the amygdala. The central nucleus of the amygdala is the main source of efferent connections to brain stem and hypothalamic structures modulating a wide range of endocrine and autonomic responses (Davis, 1992). The caudal OFC receives information from the central nucleus of the amygdala and, in return, projects directly to this nucleus, procuring thereby a circuit through which the OFC may directly modulate the activity of the amygdala. The medial and lateral OFC send extensive connections to the lateral hypothalamus, suggesting that these OFC areas are particularly involved in the regulation of visceral responses to stimuli and events. Furthermore, the OFC has also strong links with the anterior temporal pole, the insular cortex, and the LPFC (Cavada et al., 2000; Morecraft et al., 1992). Clinical neuropsychological studies indicate that the OFC exerts an inhibitory control to protect goal-directed behavior from interference (Fuster, 1999; Roberts and Wallis, 2000). Damage to the OFC leads to a *frontal lobe syndrome* (Silver and Yudofsky, 1987) or *pseudopsychopathic syndrome* (Stuss and Benson, 1984) that is characterized by distractibility, impulsivity, emotional outbursts, shallowness, argumentativeness, verbal and physical aggressiveness, hypersexuality, hyperphagia, lack of concern of consequences of behavior, failure to observe social and moral rules, and risky decision-making behavior. Individuals with OFC lesions tend to be unpredictable, their humor is labile, and they often display inappropriate and childish humour. Interestingly, these individuals show abnormal autonomic responses to emotional elicitors, difficulty to experience emotion related to situations that would normally evoke emotion, and impaired understanding of the adverse consequences of detrimental social behaviors (Damasio et al., 1990).

2.4. Sadness in children

Children begin to regulate very early (even as infants and toddlers) the stress generated by emotions and emotional situations. For instance, 18-months-olds self-soothe when their mothers are absent (Mangelsdorf et al., 1996). To be able to consciously and voluntarily self-regulate emotion, a child must be first aware of having an emotional experience, that is, this child must interpret and evaluate her perceived emotional state (Lewis, 1998). To have an emotional experience – a set of internal events – this child must be cognitively able to make reference to the fact that it is ''I'' to whom these internal events are happening. This child must also interpret these events in the context of the meaning systems that she has acquired through interactions with others. Indeed, children learn strategies for controlling their emotional responses in agreement with the social rules of their culture. These capacities involve the development of self-consciousness, a critical meta-cognition involving the idea of a referencing self (''idea of me'') (Lewis, 1995). There is some evidence that self-consciousness emerges at around 15–18 months. It is the emergence of this referencing self which allows the child to monitor and react to her emotional state, i.e., to self-reflect on her thoughts, emotions, and behavior. Cognitive development and social development thus play a pivotal role in the evolution of the capacity to regulate emotion (Cole et al., 1994).

Emotional self-regulation begins with the control of distress. Infants aged 8–18 months respond with distress and negative affect to brief separation with the mother. Between 19 and 24 months there is a significant reduction of negative emotional responses to brief maternal separation. Fox et al. (2001) have speculated that changes in response to this event during the second year of life may be the result of an infant's increasing capacity to recognize, define, and represent the cause of distress; to appraise the contextual features of the emotion elicitor; to maintain a cognitive representation of his/her mother during her absence; and to form a plan for a sequence of actions in order to modify the situation so that distress is diminished. Additionally, the infant must suppress the negative affect and distress that were elicited earlier in life by brief separation from the mother. Results of EEG studies conducted by Fox et al. (2001) have evidenced an important role for the PFC – ''the repository of the most advanced and civilized functions of the brain'' (Filley, 1995, p. 5) – in the regulation of negative affect and emotional distress. Fox and Bell (1990) have hypothesized that a combination of neurobiological maturation in the PFC and social learning experiences underlie the emergence of emotional self-regulation. Regarding this issue, during the first 6 months, the young infant's emotional regulatory capacity advances from a primarily reflexive response to physiological stimuli (e.g., thirst, hunger, pain, fatigue, etc.) to a nascent awareness of internal state and the ability to temporally associate emotional states with specific external stimuli (Kopp, 1989). By 6–8 months of age, emotional regulation begins to involve typical PFC functions, such as selective attention to stimuli and perception of temporal contingent sequences implicating the infant's own actions and external stimuli. These functions allow the infant to regulate states of emotional arousal, for instance, by signalling to caregivers to act in response to his/her emotional states. With the emergence of self-consciousness and intentionality (or goal-directedness), emotional regulatory capacities augment markedly during the second half of the first year of life. Emotion regulation then becomes truly emotional *self*-regulation, i.e., more conscious and self-guided. At this stage, the infant acquires new cognitive executive capacities (e.g., representational thought, self-monitoring, working memory, goal formulation, flexibility of responding internalization of rules to guide behavior, response

inhibition, attentional control, planning) that critically depend on PFC development (Dawson et al., 1992) and allow her to engage in intentional self-regulatory behaviors.

Phylogenetically as well as ontogenetically, the PFC is one of the last neocortical regions to develop. Evolutionarily, the PFC achieves maximal relative growth in the human brain, where it represents approximately one-third of the total volume of the neocortex. In the normal human individual, full PFC maturation is not reached until late adolescence/early adulthood (Fuster, 1999). Indeed, myelination and dendritic development occur later in the human PFC than in other cortical regions. Synaptogenesis reaches a plateau between the ages of 1 and 7 and declines through adolescence to the adult level (Bourgeois et al., 1994; Huttenlocher, 1994; Rakic et al., 1994). This decrease in synaptic number coincides with the continued development of cognitive capacities (Caviness et al., 1996). Furthermore, cortical gray matter volume achieves its peak at around 5 years of age and decreases from that time forward, while the white matter volume increases constantly until about the age of 20 years (Pfefferbaum et al., 1994). With respect to PFC myelination, Yakovlev and Lecours (1967) have postulated that it might continue well into the third decade of life. Of note, Fox et al. (2001) have emphasized the obvious similarities between the disinhibited behaviors of adults following damage to the PFC and the emotional reactions and behaviors of normal infants and young children. The cognitive and emotional changes following PFC damage have been attributed to a disruption in the inhibitory control normally exerted by the PFC on subcortical limbic structures such as the hypothalamus and the amygdala. In line with this, Posner and Rothbart (1998) have postulated that emotional self-regulation likely involves the interaction of the midfrontal ACC region with the amygdala.

Within a neurodevelopmental perspective, the fMRI protocol described in the preceding section (Lévesque et al., 2003) was used to study the neural substrates of conscious and voluntary regulation of sadness in 14 healthy girls (age range: 8–10, mean age: 9) (Lévesque et al., 2004). As in the Lévesque et al. (2003) study, the mean level of reported sadness was significantly higher in the sad condition than in the suppression condition. With regard to functional brain activity, significant loci of activation were seen in the sad condition in the left VLPFC (BA 47) and, bilaterally, in the midbrain and anterior temporal pole (BA 21). In the suppression condition, significant loci of activation were noted, bilaterally, in the LPFC (BA 9 and 10), OFC (BA 11), medial prefrontal cortex (MPFC) (BA 10), and rostral ACC (BA 24). A certain portion of the rostral ACC is connected to the OFC (Devinsky et al., 1995) and has outflow to autonomic, visceromotor, and endocrine systems. The co-activation of the rostral ACC and the OFC, while girls were attempting to suppress sadness, strongly suggest that these prefrontal regions are part of a neural circuit involved in the regulation of primary emotions. It is also worth mentioning that that a region of the MPFC close to that identified in this study, during the suppression condition, has previously been postulated to be implicated in theory-of-mind tasks (inferences about the mental states of others) (Fletcher et al., 1995) and metacognitive representation of one's own emotional state (Reiman et al., 1997; Lane, 2000). This cortical region receives sensory information from the body and the external environment via the OFC (Barbas, 1993; Carmichael and Price, 1995), and is heavily interconnected with limbic structures such as the amygdala, ventral striatum, hypothalamus, midbrain periaqueductal gray region, and brainstem autonomic nuclei (Barbas, 1995; Carmichael and Price, 1995). Such anatomical relationships suggest a role for this area of the MPFC in the integration of the visceromotor aspects of emotional processing with information gathered from the internal and external environments. It thus seems plausible that the MPFC activation noted in girls, during the suppression task, related to ''reflective conscious awareness'' (awareness of awareness) (Farthing, 1992).

Voluntary down-regulation of sadness was subjectively more difficult for children than adults in the Lévesque et al. (2003) study. As for the brain regions activated in both studies, the suppression task recruited more prefrontal areas in children than in adults. In addition, the spatial extent of the LPFC activation was five-fold greater in children than in adults. These differences suggest that voluntary suppression of a primary emotion, such as sadness, requires more prefrontal work in children than in adults. In agreement with this, it has been demonstrated that children show greater volume of PFC activity than adults when performing tasks requiring active maintenance and/or suppression of different types of information (e.g., go no-go paradigm) (Casey et al., 1995; Cohen et al., 1994). Casey and colleagues have proposed that such differences may reflect maturational differences with respect to the PFC. Along the same lines, it appears reasonably fair to assume that conscious and voluntary self-regulation of emotion is more challenging (cognitively and affectively) in children than in adults because the maturation of the prefronto-subcortical (limbic) connections is not yet completed.

2.5. Self-regulation of negative pictures

To date, several fMRI studies of emotional self-regulation have been conducted by other research teams. One of these studies (Schaefer et al., 2002) used an event-related design to test the hypothesis that voluntary regulation of emotionally negative pictures is associated with modifications in neural activity within the amygdala, a cardinal component of emotion perception. Negative and emotionally neutral pictures selected from the International Affective Picture System (IAPS) (Lang et al., 1998) were presented to seven healthy female volunteers. Volunteers were instructed to either maintain the initial emotional response induced by the picture throughout its presentation or passively view the picture without regulating the emotion. After each picture presentation, volunteers indicated how they currently felt using a Likert-type scale. Volunteers reported feeling more negative during negative picture trials than neutral picture trials. Volunteers also reported feeling more negative on maintain trials than view trials. In agreement with previous functional neuroimaging studies having shown increased activation in the amygdala in response

to emotionally negative stimuli, greater amygdalar signal change was noted during the presentation of negative compared to neutral pictures. Increased activation in the amygdala was associated with maintenance of negative emotion compared to the passive viewing condition. Moreover, a prolonged BOLD signal increase was found in the amygdala when volunteers maintained the negative emotional state during the presentation of negative pictures. This amygdalar signal increase was significantly correlated with volunteers' self-reported levels of negative emotion. These findings suggest that the conscious cognitive processes that modulated the emotional responses of the volunteers to the negative pictures were associated with an alteration of the degree of neural activity within the amygdala, i.e., the degree of amygdalar activity can be consciously and voluntarily regulated. In keeping with this, Hariri et al. (2003) have recently demonstrated, using fMRI, that whereas perceptual processing of threatening and fearful non-face (IAPS) stimuli was associated with a bilateral amygdala response, cognitive appraisal of the same stimuli was associated with a reduction of this amygdala response and a concomitant increase in response of the right prefrontal and anterior cingulate cortices.

In another event-related fMRI study (Ochsner et al., 2002), ''reappraisal'' was used as a cognitive strategy to modulate emotional experience. Reappraising a negative event in non-emotional terms allows reducing unpleasant emotion with few of the subjective, cognitive, and physiological negative consequences associated with some other emotion-regulatory strategies (1998, 2002; Jackson et al., 2000; Richards and Gross, 2000). Ochsner et al. (2002) hypothesized that the neural circuits and processing dynamics implicated in the cognitive control of emotion would be similar to those involved in other forms of cognitive control. In their study, negative and neutral pictures from the IAPS were presented to 15 healthy female volunteers. For each trial volunteers were instructed to view the picture and allow themselves to experience/feel any emotional response it might elicit. The picture remained on the screen for an additional period of time with an instruction either to attend or Reappraise. On attend trials, volunteers were requested to attend to and be aware of, but not to try to modify, any feelings induced by negative or neutral pictures. On reappraise trials, volunteers were instructed to reinterpret the negative picture so that it no longer generated a negative emotional response. After the presentation of each picture volunteers had to rate on a four-point scale the strength of current negative emotion. Behaviorally, reappraisal of negative pictures successfully lessened negative emotion. The average ratings of the strength of negative emotion were significantly lower on reappraise trials than on attend trials. Neurally, reappraisal was associated with a significant activation of the dorsal and ventral regions of the left LPFC (BA 6, 8, 10, 44, 46) as well as the dorsal MPFC (BA 8). In addition, the right amygdala was significantly more activated on attend than reappraise trials. Interestingly, the medial orbitofrontal cortex (MOFC) (BA 11) displayed greater activation to most negative pictures on attend than on reappraise trials, whereas activated areas of the LPFC showed the opposite trend. For one of these areas, the ventral LPFC (VLPFC), increased activation during reappraisal was correlated across volunteers with decreased activation in amygdala.

For Ochsner et al. (2002), these results provide good evidence that reappraisal may modulate the emotion processes implemented in the amygdala and MOFC and involved in the evaluation of the emotional significance and contextual relevance of a stimulus (or event). The specific LPFC and MPFC areas found associated with reappraisal were comparable to the prefrontal areas frequently seen activated in diverse working memory and response-selection tasks that entail resisting to interference from competing stimuli and maintaining information in awareness (Cabeza and Nyberg, 2000; Courtney et al., 1998; Smith and Jonides, 1999). This similitude strongly suggests that a common ensemble of LPFC and MPFC areas underlie the cognitive regulation of both feelings and thoughts (Knight et al., 1999; Miller and Cohen, 2001; Ochsner and Feldman Barrett, 2001; Smith and Jonides, 1999). The fact that the ventral LPFC activation was inversely correlated with the activation of the amygdala and MOFC indicates that the VLPFC may play an important role in conscious and voluntary regulation of emotion processes. Furthermore, the modulation of the neural activity within the amygdala and the MOFC supports the view that reappraisal can influence processes involved in the evaluation of the emotional significance of a stimulus (Anderson and Phelps, 2001; Whalen et al., 1998), as well as those implicated in the evaluation of the significance of that stimulus with reference to current contextual meaning (which is determined by situational or personal goals) (Kawasaki et al., 2001; Ochsner and Feldman Barrett, 2001; O'Doherty et al., 2001; Bechara et al., 2000; Elliott et al., 1997). Ochsner et al. (2002) postulated that the reappraisal processes implemented by lateral and medial prefrontal regions may play an important role in the regulation of evaluation processes associated with the OFC. This cortical region may be responsible for the selection of appropriate, and the transient suppression of inappropriate, emotional responses. Because the LPFC and the amygdala have few direct anatomical connections, Ochsner et al. (2002) further contended that the LPFC could influence the amygdala via the MOFC, which has reciprocal connections with both structures (Cavada et al., 2000). By directly modulating the representations of the emotional salience of a stimulus in the MOFC, activation in the LPFC could indirectly down-regulate processing in the amygdala.

More recently, Ochsner et al. (2004) conducted another fMRI study in 24 healthy female volunteers to compare the neural systems supporting down- and up-regulation, with reappraisal, of negative emotion induced by IAPS pictures. Results indicated that: (1) amygdala activation was modulated up or down in agreement with the regulatory goal; (2) up-regulation recruited the ACC (BA 32), MPFC (BA 9, 32), left LPFC (BA 9), and left amygdala; and, (3) down-regulation recruited the left LPFC (BA 8, 9) and left lateral OFC (BA 47). For Ochsner et al. (2004), these results suggest that both common and distinct neural systems underlie various forms of reappraisal. These results further indicate that which specific

prefrontal systems modulate the amygdala is contingent on the regulatory goal and strategy used.

Lastly, Phan et al. (2005) scanned 14 healthy male and female volunteers while they down-regulate via reappraisal negative IAPS pictures. Online subjective ratings of intensity of negative affect were used as covariates of brain activity. Down-regulation of negative affect was associated with activation of dorsal ACC (BA 32), right dorsal MPFC (BA 9), and right LPFC (BA 9), and attenuation of brain activity within the left amygdala vicinity. Moreover, activity within right dorsal ACC (BA 32) was negatively correlated with intensity of negative emotion, whereas activation of the amygdala was positively correlated with intensity of negative emotion. These findings highlighted a functional dissociation of corticolimbic brain responses, implicating enhanced activation of PFC and attenuation of limbic areas, during voluntary down-regulation of negative emotion.

3. Neuroimaging studies of psychotherapy

3.1. Obsessive-compulsive disorder

In a seminal study (Schwartz et al., 1996), nine patients with obsessive-compulsive disorder (OCD) were studied during resting state with positron emission tomography (PET) before and after 10 weeks of structured exposure and the four-step cognitive-behavioral treatment method developed by Schwartz (Schwartz and Begley, 2002). The goal of this treatment method is to teach OCD patients to respond to the intrusive thoughts and urges which comprise the core symptoms of OCD in a new and more adaptive way. The first step involves teaching patients to relabel the intrusive thoughts and urges as symptoms of the brain disorder OCD. In the second step, patients are encouraged to reattribute the bothersome and persistent nature of the symptoms to 'false messages' coming from a dysfunctional brain. The goal of the first two steps is to produce a modification in perspective concerning OCD symptoms, which results in patients profoundly appreciating the fact that they have a critically important choice to make regarding their behavioral responses in the moments after symptoms intrude into consciousness. In the third step, patients learn to change behavioral responses while the uncomfortable intrusive thoughts and urges are still present. In the fourth step, patients come to revalue the intrusive thoughts and urges as much less important and noteworthy, and the fear and anxiety associated with them gradually disappear. One aspect of this training that is particularly crucial is mindfulness (or mindful awareness), i.e., the ability to observe one's own mental phenomena with the calm clarity of an ''impartial spectator'' (Nyanaponika, 2000). This ability allows the patient to create a distance between her experience of the self and her experience of the OCD symptoms, and increases the patient's capacity to choose how to respond to intrusive thoughts and urges.

Treatment responders showed significant bilateral decreases in caudate glucose metabolic rates that were greater than those seen in poor responders to treatment. Before treatment, there were significant correlations of brain activity, in the right hemisphere, between the orbitofrontal gyrus and the head of the caudate nucleus, and the orbital gyrus and the thalamus. These correlations diminished significantly after effective treatment. These results suggested that a prefronto-cortico-striato-thalamic brain system is involved in the mediation of OCD symptoms. Importantly, these results demonstrated that psychotherapy could produce significant changes in brain activity.

3.2. Panic disorder

The effect of cognitive-behavioral therapy (CBT) has also been investigated during resting state with [^{18}F]-2-fluoro-deoxy glucose (^{18}FDG) PET scanning in six patients suffering from panic disorder (Prasko et al., 2004). The severity of panic disorder was measured with Panic Disorder Severity Scale (PDSS). The therapy was a six-week standard group treatment program for panic disorder (three group sessions per week, each lasting one and a half hour) consisting of education and corrective information, cognitive restructuring, training in diaphragmatic breathing and relaxation, and in vivo exposure and problem solving. Repeat ^{18}FDG PET scanning was carried out after a three month period. The scores of the PDSS significantly diminished. ^{18}FDG uptake decreases were measured in the right inferior temporal (BA 42) gyrus, superior (BA 10) and inferior (BA 45) frontal gyri, whereas ^{18}FDG uptake increases were detected mostly in the left hemisphere, in inferior frontal gyrus (BA 9), middle temporal gyrus (BA 21), and insula (BA 13). These results suggest that effective CBT can positively alter brain metabolism in individuals with panic disorder.

3.3. Unipolar major depressive disorder

So far a few neuroimaging studies have been conducted during resting state to measure the impact of psychotherapy on brain function of individuals with unipolar major depressive disorder (MDD). In the first of these studies, 13 patients with MDD (four males and nine females) were scanned with 99mTc-HMPAO SPECT (Martin et al., 2001). After this initial scan, patients had six one-hour weekly sessions of interpersonal psychotherapy (IPT). IPT is a brief form of psychotherapy that addresses interpersonal issues in depression. IPT teaches depressed patients strategies to change interpersonal problems.

SPECT scans and clinical assessments (using the DSM-IV and the 17-item Hamilton Depression Rating Scale – HAM-D) were repeated at six weeks. Results showed that depressed symptoms decreased significantly. Limbic right posterior cingulate and right basal ganglia activations were noted after IPT. These results indicate that IPT can increase blood flow in the basal ganglia and limbic system in patients with MDD.

Brody et al. (2001) also investigated the impact of IPT on regional cerebral metabolic activity in patients with unipolar MDD. Fourteen MDD patients and 16 normal control volunteers underwent ^{18}FDG PET scanning before and after 12 weeks. MDD patients were treated with IPT between the initial and repeat scans while control volunteers received no

treatment. The initial ^{18}FDG PET scan demonstrated that MDD patients had higher metabolism than control volunteers in the PFC, caudate and thalamus, while lower metabolism was found in the anterior inferior temporal lobe. These results are consistent with those of neuroimaging studies of MDD showing regional metabolic abnormalities in the PFC, anterior cingulate gyrus, and temporal lobe. Following IPT, MDD patients had metabolic changes in the direction of normalization in these brain regions. Symptomatic improvement (assessed with the 17-item HAM-D) was associated with significant decreases in the right PFC and left anterior cingulate gyrus, and significant increases in left temporal lobe. Specifically, metabolism increased in left temporal lobe and anterior insula, and decreased in right middle frontal gyrus (including both VLPFC and DLPFC), right dorsal caudate and left middle ACC. Normal control volunteers had no significant changes in these brain regions. These results indicate that IPT can normalize regional brain metabolic abnormalities found in MDD patients. It has been postulated that psychotherapy leads to changes in synaptic plasticity (Liggan and Kay, 1999; Post and Weiss, 1997). Since IPT seeks to improve socialization, Brody et al. (2001) proposed that brain regions related to socialization, such as the ACC, may undergo a reduction of neuronal connectivity during IPT.

Goldapple et al. (2004) examined, using ^{18}FDG PET, the brain changes associated with CBT in unipolar MDD patients. Seventeen unmedicated outpatients were scanned before and after a 15- to 20-session CBT treatment. During this treatment, patients learned several behavioral and cognitive strategies aiming to combat dysphoric mood and reduce automatic reactivity to negative thoughts and attitudes. Patients were taught cognitive monitoring to dismantle ostensibly complex chains of thinking and feeling into separate elements. Behaviorally, patients were asked to increase the frequency of pleasant events in their lives. Between sessions, patients were requested to record their thinking using thought records and to test their interpretations and beliefs via behavioral experiments. Significant clinical improvement (measured with the 17-item HAM-D) was noted in the 14 study completers. This improvement was associated with increases in hippocampus and dorsal ACC (BA 24), and decreases in dorsal (BA 9/46), ventral (BA 47/11), and medial (BA 9/10/11) PFC. These results suggest that CBT influences clinical recovery by modulating the functioning of selective areas in limbic and cortical regions. Remarkably, the prefrontal decreases seen with CBT response in the Goldapple et al. (2004) study are quite similar to those reported in the Brody et al. (2001) study.

3.4. Spider phobia

So far, a few studies have been carried out to identify changes in brain activation following CBT in individuals with spider phobia. In one of these studies (Paquette et al., 2003), fMRI was used in spider phobics ($n = 12$) to measure, one week before CBT and one week after CBT, brain responses to the viewing of film excerpts depicting spiders. Normal control volunteers ($n = 13$) were also scanned (once) while they were exposed to the same film excerpts. The CBT consisted of gradual exposure-based treatment to spiders (Öst, 1996) using guided mastery (Bandura, 1997) and education for correcting misbeliefs about this animal. This approach was chosen considering the evidence suggesting that short intensive exposure sessions should be considered the method of choice for specific phobias. During four consecutive weeks, phobic volunteers met once a week with two psychotherapists for a 3 h intensive group session. During the first session, phobic volunteers were gradually exposed to an exercise book containing color pictures of spiders. During the second session, they were gradually exposed to films excerpts of living spiders. Self-exposure homework, with the exercise book and the videotape, was given between each session and was reviewed with the therapists at the next meeting. In the third session, volunteers were exposed to real spiders. During this session, a spider expert from the Montreal Insectarium provided volunteers with a lot of information about spiders, helping volunteers to correct their erroneous beliefs about this animal. The contribution of this expert represented a crucial element of the CBT. In the fourth and last session, volunteers were asked to touch a tarantula. All phobic volunteers responded successfully. Responders to CBT were defined as volunteers who were able to touch, without reporting fear reactions, the entire series of pictures depicting spiders, the TV screen showing living spiders, and the real spiders.

FMRI results showed that, in phobic volunteers before CBT, the transient state of fear triggered by the phobogenic stimuli was associated with significant activation of the right LPFC (BA 10), the parahippocampal gyrus (BA 36), and the visual associative cortical areas, bilaterally (BA 19, 20, 37). For normal control volunteers, only the left middle occipital gyrus (BA 19) and the right inferior temporal gyrus (BA 37) were significantly activated. In phobic volunteers before CBT, the activation of the LPFC may reflect the use of metacognitive strategies aimed at self-regulating the fear triggered by the spider film excerpts, whereas the parahippocampal activation may be related to an automatic reactivation of the contextual fear memory that led to the development of avoidance behavior and the maintenance of spider phobia. After successful completion of CBT, no significant activation was found in the LPFC and the parahippocampal gyrus. These findings suggest that a psychotherapeutic approach such as CBT can lead to adaptive regional brain changes in individuals with anxiety disorders.

In another fMRI study (Straube et al., 2006), brain activation to spider videos was assessed in spider phobic ($n = 28$) and healthy control volunteers ($n = 14$). Phobic volunteers were randomly assigned to a CBT group ($n = 13$) and a waiting-list control group ($n = 12$). Four treatment goals had to be fulfilled by volunteers without strong feelings of anxiety: (1) to hold a living tarantula for about 10 min; (2) to catch spiders at least 10 times with a glass at different locations within the therapy room; (3) to catch spiders at least three times in the basement of the institute where the CBT sessions were held; (4) to touch a rapid moving house spider. The two phobic groups were

scanned twice. Before CBT, brain activation did not differ between both groups of phobic volunteers. Compared to control volunteers, phobics exhibited greater responses to spider videos in the insula and ACC. CBT markedly reduced phobic symptoms in the CBT group while symptoms remained unchanged in the waiting-list control group. In the second scanning session, a significant decrease of activity in the insula and ACC was noted in the CBT group compared to the waiting-list control group (Fig. 2). These results suggested that increased activation in the insula and ACC was associated with spider phobia, whereas a reduction of these brain responses was correlated with successful therapeutic intervention.

4. Neuroimaging studies of placebo effect

4.1. Definition of placebo effect

The word placebo is Latin for 'I shall please'. Placebo refers to "any treatment —including drugs, surgery, psychotherapy and quack therapy— used for its ameliorative effect on a symptom or disease but that is actually ineffective or not specifically effective for the condition being treated" (Shapiro and Shapiro, 1997). The psychophysiological responses elicited by placebos seem to reflect a mind/body interaction that is guided by subjective factors, such as expectations, beliefs, meaning, hope for improvement, and relational parameters (Shapiro and Shapiro, 1997). The placebo effect can be very specific and this specificity depends on the information available to the recipient. For instance, a placebo will have the opposite effect on heart rhythm and blood pressure when it is given as an inhibitor than when it is administered as a stimulant. Such specificity clearly demonstrates that the placebo effect is related to the patient's beliefs and expectations.

4.2. Parkinson's disease

A progressive loss of dopaminergic neurons in the dorsal striatum (caudate and putamen) characterizes Parkinson's disease (PD). Clinically, this neurological disorder is associated with poverty of movements. Classic treatment with levodopa (L-dopa) seeks to increase the levels of dopamine in the dorsal striatum. Such increase leads to motor improvement (de la Fuente-Fernandez and Stoessl, 2004). Placebo administration has long been recognized for improving PD (Benedetti et al., 2004).

In an influential study, de la Fuente-Fernandez et al. (2001) scanned patients with PD using PET and a labelled dopaminergic agonist ([^{11}C] raclopride) which binds to dopamine D_2/D_3 receptors. The striatal raclopride binding potential of patients with PD was measured under two conditions: (1) a placebo-controlled, blinded study in which the patients did not know when they were receiving placebo or active drug (apomorphine, a dopamine receptor agonist) – all patients received both placebo and active drug; (2) an open study in the same patients without placebo (baseline). When placebo was administered, a significant decrease raclopride binding potential was found in the striatum (caudate nucleus and putamen) compared with baseline observations (Fig. 3). The decrease in raclopride binding capacity correlated with improvement in clinical symptoms. It is noteworthy that the magnitude of the placebo response was comparable to that of apomorphine. Moreover, there were no differences in the striatal raclopride binding potential between this group of patients when studied without placebo and another group of patients matched for age and severity of parkinsonism and examined solely in an open manner. These results constitute in vivo evidence for considerable release of endogenous

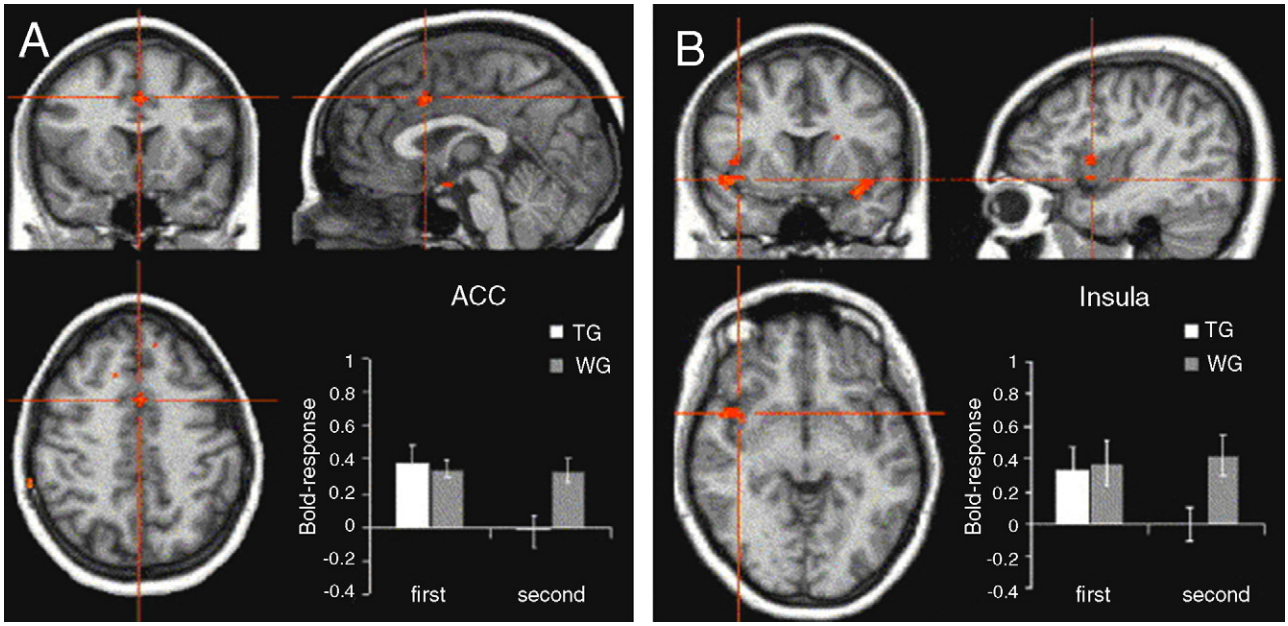

Fig. 2. BOLD signal activation of ACC (A) and insula (B) to spider versus control videos in the waiting-list group (WG) compared to the therapy group (TG) during the second but not the first scanning session (reproduced with permission of Elsevier from Straube et al., 2006).

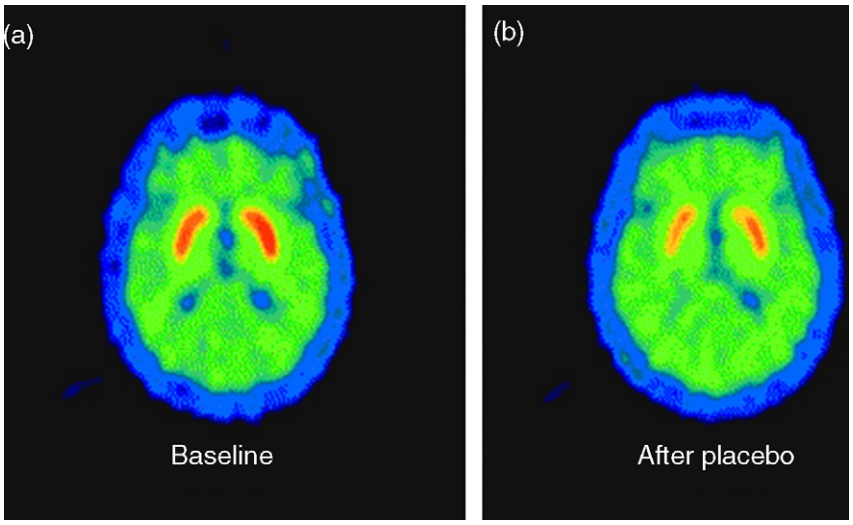

Fig. 3. [^{11}C]raclopride (RAC)–PET scans of a patient with Parkinson's disease at open baseline (a) and after placebo administration (i.e. saline injected) (b). The placebo-induced decrease in striatal radioactivity (indicated by the less intense red colour) is thought to reflect an increase in the synaptic level of dopamine, which inhibits RAC from binding to dopamine D2 receptor sites (reproduced with permission of Elsevier from de la Fuente-Fernandez and Stoessl, 2002).

dopamine in the striatum of PD patients in response to placebo. This powerful placebo effect in PD seems to be mediated by an increase in the synaptic levels of dopamine in the damaged nigrostriatal dopamine system. Noticeably, the estimated amount of released dopamine was higher in those patients who perceived a placebo effect than in those who did not.

Using the intracranial self-stimulation paradigm, Garris et al. (1999) have provided evidence that it is the expectation of the reward that elicits dopamine release in the nucleus accumbens. Based on this, and the known relationship between striatal dopamine levels and motor function, de la Fuente-Fernandez and Stoessl (2002) speculated that if the expectation of a reward triggers the release of dopamine, not only in the nucleus accumbens but also in the nigrostriatal pathway, the placebo effect in patients with PD could pertain to the expectation of clinical benefit, and could be mediated by dopamine release in the striatum. In line with this view, de la Fuente-Fernandez et al. (2001) found that the placebo response in PD patients was associated with a raclopride binding decline in the nucleus accumbens (ventral striatum) that was similar to that seen in the caudate and putamen (dorsal striatum). However, the magnitude of placebo-induced changes in the nucleus accumbens was not significantly different between patients who experienced clinical benefit and those who did not, contrary to the results from the dorsal striatum. Because they assume that the perception of clinical benefit must be rewarding, de la Fuente-Fernandez and Stoessl (2002) have proposed that dopamine is released within the ventral striatum with respect to the expectation of reward (i.e., the expectation of clinical benefit) rather than the reward itself (i.e., the perception of clinical benefit).

Pollo et al. (2002) have examined how opposite expectations of bad and good motor performance influence the therapeutic effect of sub-thalamic nucleus (STN) stimulation in seven PD patients who had undergone chronic implantation of electrodes for deep brain stimulation. The STN plays a central role in the functioning of basal ganglia. A double-blind experimental design was used to test each patient twice in different days, with an interval of one week. Neither the patient nor the experimenter knew the intensity of the stimulation delivered. In both conditions B (bad performance) and G (good performance), the stimulus intensity was modified with the same gradation and the movement velocity of the right hand was measured. In condition B (bad), stimulation was reduced from 80% to 20% and patients were told that motor performance was going to worsen. In condition G (good), patients were told that nothing was going to change in their motor performance, so that no worsening was expected when the stimulation was reduced from 80% to 20%. When the stimulus was increased from 20% to 40%, patients were instructed that a major improvement in motor performance was going to occur because of a marked increase of STN stimulation. Results showed that when the stimulation of the STN was reduced to 20% of initial stimulation, the worsening of the movement velocity over a 30 min period was present only in condition B. When the stimulation was increased to 40%, the effects of the stimulation were significantly better in condition G than in condition B. These results demonstrate that movement velocity in response to STN stimulation can be modulated by different expectations of motor performance. These results also indicate that expectations about motor performance induce neural changes very rapidly.

In another double-blind study about the placebo effect in PD, Benedetti et al. (2004) recorded in nine patients with PD the activity from single neurons in the STN, before and after placebo administration, to see whether changes in neuronal firing rates were related to the placebo response. Neuronal activity recorded from neurons in one STN before placebo administration was used as a control. After the placebo – a subcutaneous injection of saline solution along with the verbal suggestion of a motor improvement – neuronal activity was recorded from neurons into the other STN. A placebo response

was defined as the decrease of arm rigidity. PD patients who showed a clear clinical placebo response also showed a significant decrease in neuronal firing rates compared to the pre-placebo STN. A no-treatment group was also studied to address the possibility that the difference in neuronal firing rates between the pre- and post-placebo STN was not related to the placebo treatment itself. No significant difference between the neuronal firing rates of the two STNs was found, suggesting that the difference between the first and the second side of implantation in the placebo group was linked to the placebo intervention *per se*.

4.3. Unipolar MDD

The placebo effect plays an important role in controlled short-term clinical trials of antidepressants (Shapiro and Shapiro, 1997). To learn more about the functional brain correlates of this effect, Mayberg et al. (2002) used FDG PET to measure changes in regional brain glucose metabolism in 17 patients with unipolar MDD who were participating in a randomized double-blind placebo-controlled study of the antidepressant fluoxetine. Common and unique response effects to the administration of placebo or fluoxetine were evaluated after a six-week trial. FDG PET scans were acquired before treatment (baseline) and after one and six weeks of treatment. Clinically, symptom remission was seen in eight of the 15 study completers. Four of the eight responders had been treated with fluoxetine and four with placebo. For the responders in both groups, clinical response at the end of the six-week trial was associated with increases in prefrontal (BA 9/46), parietal (BA 40), and posterior cingulate (BA 31) cortices, and decreases in subgenual cingulate cortex (BA 25), parahippocampus, and thalamus. Fluoxetine response was accompanied by additional increases in pons and decreases in caudate, insula, and hippocampus. No changes in regional brain glucose metabolism were unique to placebo at six weeks. These results demonstrate that placebo can produce metabolic changes in specific cortical and paralimbic regions that are relatively comparable to those of fluoxetine, a selective serotonergic reuptake inhibitor known to uplift mood and diminish dysphoria.

4.4. Placebo analgesia

At least some aspects of placebo analgesia depend upon the endogenous opioid system given that this effect can be blocked by the administration of the opioid antagonist naloxone (see, for instance, Levine et al., 1978). This effect of naloxone suggests that placebo analgesics can stimulate the release of endogenous opioids. The brainstem and the rostral ACC (rACC)/ventromedial PFC are known to be involved in opioid analgesia (Fields and Basbaum, 2000). Recently, Petrovic et al. (2002) used PET to determine whether these cerebral structures are also implicated in placebo analgesia. Nine healthy volunteers participated in the study. The analgesic effects of a placebo treatment (saline) and a rapidly acting opioid (remifentanil) were compared in a pain-stimulus paradigm. Drugs were injected intravenously. Six different conditions were utilized: heat pain and opioid treatment; nonpainful warm stimulation and opioid treatment; heat pain and placebo treatment; nonpainful warm stimulation and placebo treatment; heat pain only; and nonpainful warm stimulation only. To induce placebo responses (expectation of pain relief), volunteers were told that each of the drugs was a potent analgesic. The placebo treatment was also preceded by active opioid during noxious stimulation. The opioid agonist remifentanil was associated with rCBF increases in the rACC and lower brainstem. Pain intensity rating during the placebo condition decreased in most volunteers, compared to the pain condition. The placebo analgesia (heat pain and placebo treatment vs. heat pain only) was accompanied by increased rCBF in the orbitofrontal regions, bilaterally, and the contralateral rACC. These results support the view that the rACC is involved in the analgesic response mechanism during placebo. Furthermore, these results and a significant covariation in activity between the rACC and the pons during the placebo condition suggest that the rACC might play a central role in the cortical control of the brainstem during placebo analgesia (Petrovic et al., 2002).

Wager et al. (2004) carried out two experiments ($n = 24$ and $n = 23$) with fMRI to investigate the neural mechanisms underlying the effects of expectations of placebo analgesia. In the first experiment, which consisted of five blocks of 15 trials, volunteers were scanned while they received painful and nonpainful electric shocks to their right wrist. After each trial, volunteers rated the intensity of the shock on a 10-point scale. Volunteers received shocks without any treatment during the first block. After Block 1, a skin cream was applied to the volunteer's right wrist. Half the volunteers were instructed that this was an analgesic cream that would decrease but not eliminate the pain elicited by the shocks. After Blocks 2 and 3 were finished (placebo condition), the cream was removed and the same cream was reapplied. Volunteers were then told that the cream was a different, ineffective cream. Blocks 4 and 5 were completed (the order of placebo and control conditions were reversed for the other half of the volunteers). The behavioral and neural measures of the placebo effect were the differences in ratings of pain and regional brain activity in the control versus placebo conditions. In the second experiment, thermal stimuli were applied to different patches of skin on the left forearm. These patches of skin were treated with identical placebo and control topical creams. Pain responses were analyzed in three separate segments (early, peak, and late). During the calibration phase, stimuli were varied to identify temperatures corresponding to reported pain levels of 2, 5, and 8 on a 10-point scale. In the following manipulation phase, pain was surreptitiously decreased in the placebo condition. Volunteers were told that the blocks of stimuli administered to the placebo-treated patch of skin or the control-treated patch were at level 8. Still, thermal stimuli were applied at level 2 in the placebo-treated patch and at level 8 in the control-treated patch. Lastly, additional blocks of stimuli were delivered to placebo- and control-treated patches of skin during the test phase. Volunteers were told that these stimuli were at level 8, but both were applied at level 5.

In Experiment 1, the placebo treatment significantly decreased reported pain in over 70% of volunteers. Placebo reduced the brain responses in a number of brain regions known to be implicated in the subjective experience of pain, such as the rACC, anterior insula, and thalamus (contralateral to stimulation) (Craig et al., 2000). Moreover, the magnitude of the reduction between control and placebo trials in reported pain significantly correlated with the magnitude of reduction in neural activity during the shock period in the rACC, contralateral insula, and contralateral thalamus. In Experiment 2, placebo-induced increases in DLPFC were correlated with placebo-induced reductions during pain in contralateral thalamus, insula, and rACC. Correlations were also found between placebo increases in OFC and placebo reductions in pain activity in the thalamus, insula, and rACC. These results are consistent with the hypothesis that placebo manipulations reduce neural responses in pain-responsive regions. These results also support the hypothesis that DLPFC activation represents a form of externally induced top-down control that regulates the experience of pain.

In another study, Lieberman et al. (2004) used PET to scan patients with irritable bowel syndrome (IBS) before and following three weeks of receiving a placebo treatment. IBS is characterized by chronic, recurrent abdominal pain and discomfort associated with altered bowel habits. On scan day 1, patients were scanned at rest and during controlled rectal stimulation, which produces physical discomfort similar to IBS symptoms. Following this pre-placebo scan, patients were given pharmacologically inactive pills to take on a daily basis for the next three weeks. They were told that the pill might decrease their IBS symptoms. Patients kept a symptom diary starting a week before scan day 1 and continuing throughout the 3 weeks of placebo administration. On scan day 2, patients were again scanned at rest and during rectal stimulation. A robust positive correlation was found between pre- to post-placebo rCBF increases in the right VLPFC and subjective reports of symptom improvement. Connectivity analyses revealed that increased activity in the right VLPFC was associated with decreased activity in dorsal ACC (dACC), which was negatively correlated with symptom improvement. According to Lieberman et al. (2004), activation of the right VLPFC was associated with the positive expectations related to the placebo treatment (i.e., ''I believe I am going to be less bothered by pain now'').

Zubieta et al. (2005) used PET and [^{11}C]carfentanil, a μ-opioid receptor-selective radiotracer, to investigate whether a placebo with expectation of analgesia can activate the endogenous opioid system. Under these conditions, activation of this system is manifested by reductions in the *in vivo* availability of synaptic μ-opioid receptors to bind the radiolabeled tracer. A blind, randomized and counterbalanced design was utilized to introduce pain and pain + placebo (administration of physiological saline) conditions. A baseline scan study was carried out without any intervention. The second and third scans included either a sustained pain challenge, or sustained pain with placebo with implied analgesic properties. Deep sustained muscle pain was produced by the infusion of hypertonic saline into the masseter muscle. Volunteers were requested to assess the expected analgesia prior to the introduction of the placebo and afterwards, estimating the analgesic properties using a visual analog scale ranging from 0 (no analgesic effect) to 100 (maximum analgesia). Significant effects of placebo on μ-opioid system activation were found in the left (ipsilateral to pain) DLPFC (BA 8 and 9), pregenual rostral right (contralateral) ACC (BA 24 and 25), right (contralateral) anterior insular cortex, and left (ipsilateral) nucleus accumbens. DLPFC endogenous opioid activity was significantly correlated with the magnitude of analgesia expected by the volunteers before placebo administration. These results provide evidence that a placebo treatment with implied analgesic properties activates the endogenous opioid system via the μ-opioid receptors. These results also indicate that the expectations of the perceived analgesic efficacy of the placebo are mediated by endogenous opioid neurotransmission in the DLPFC (Zubieta et al., 2005).

Zubieta et al. (2006) used PET and [^{11}C]carfentanil and a design similar to that utilized in their 2005 study to test the hypotheses that levels of expectation of analgesia and the subjective experience of pain both influence the activation of endogenous μ-opioid neurotransmission during the introduction of a placebo intervention. Expectation of analgesia prior to the placebo intervention and the analgesic effectiveness of the placebo were rated at 51%. Reductions in the binding potential measure after placebo were observed in 14 out of 19 volunteers in the DLPFC, 12 out of 19 volunteers in the pregenual ACC, 13 of the 19 volunteers in the anterior insular cortex, and 11 out of 19 volunteers in the nucleus accumbens. The emotional state of the individuals during pain, or the affective quality of the pain experienced, were significantly associated with placebo-induced endogenous opioid responses in the DLPFC, anterior insular cortex, and nucleus accumbens. These results suggest that the internal affective state of the individuals during pain contributes also greatly to endogenous opioid mediated placebo analgesic responses.

4.5. Psychostimulant expectation

In healthy humans, Kaasinen et al. (2004a) have shown that moderate doses of oral caffeine induce decrease of thalamic [^{11}C]raclopride binding, an indirect indicator of dopamine release (Kaasinen et al., 2004a). These researchers have also conducted another [^{11}C]raclopride PET study in healthy human volunteers, this time to investigate dopaminergic effects in psychostimulant expectation. Eight habitual coffee drinkers were scanned after no treatment and after oral placebo tablets in a counter-balanced setting. During the placebo condition the volunteers were told that they had a 50% chance of receiving caffeine, but they all received placebo. The placebo produced a significant bilateral dopamine release in the thalamus, which was reflected by a 15% reduction in thalamic [^{11}C]raclopride binding as compared with no treatment. The tracer binding in the putamen correlated positively with the level of arousal after placebo. These results demonstrate that caffeine expectation induces dopaminergic placebo effects. Since these effects are

comparable to previous findings with oral caffeine (Kaasinen et al., 2004b), it appears that caffeine and placebo caffeine share some dopaminergic mechanisms of action.

4.6. Placebo in emotional processing

Petrovic et al. (2005) recently conducted an fMRI study to test the hypothesis that placebo treatment can modulate emotional perception. This study was performed on two consecutive days. On day 1, volunteers were presented with three blocks of mixed unpleasant and neutral pictures. Volunteers were asked to rate the unpleasantness of the unpleasant pictures at the end of each presentation block. After the first presentation in which no drugs had been administered, volunteers were given intravenously a low dose of benzodiazepine, which markedly reduced the unpleasantness rating the second presentation. This effect was totally reversed in the third presentation by pre-treating the volunteers with a benzodiazepine receptor antagonist. Before each block, volunteers were informed of the possible effect of the anxiolytic and the anxiolytic blocker drugs on their perception of emotions. Volunteers were also told that both these drugs would be used on day 2 during the fMRI experiment. Therefore, a strong expectation of the treatment effect was induced. On day 2, volunteers were instructed that they would be treated either with the anxiolytic drug or the anxiolytic blocker prior to presentation of unpleasant and neutral pictures. Volunteers were also informed via a computer screen about the upcoming treatment before each block began. This time, however, volunteers received intravenous saline before each block instead of being treated with the active drugs. Thus, the placebo effect was induced (expectation of anxiolytic effect) when volunteers believed that they had received the anxiolytic drug, and the control effect was induced (no expectation of anxiolytic effect) when volunteers believed that they had received the anxiolytic blocker. Volunteers were scanned during four different conditions: (1) unpleasant pictures after placebo treatment; (2) neutral pictures after placebo treatment; (3) unpleasant pictures after control treatment; and (4) neutral pictures after control treatment. Behaviorally, there was a strong decrease in the subjective rating of unpleasantness for the placebo conditions as compared to control conditions. For the placebo responders, the activity in extrastriate visual areas was significantly reduced in the placebo condition compared to the anxiolytic blocker condition for the unpleasant pictures. In addition, a correlation was found between the degree of change in unpleasantness rating due to placebo treatment and the suppression of placebo-dependent activity in the visual areas and amygdala/para-amygdaloid complex. Activation of the right lateral OFC (LOFC), rACC, and VLPFC was also detected in placebo responders during the placebo response. Since a similar network has previously been shown to be activated in placebo analgesia (Petrovic et al., 2002), Petrovic et al. (2005) concluded that modulatory processes in placebo are not specific for placebo analgesia, but are rather a part of the mechanisms generally implicated in emotional self-regulation, including instances of cognitive modulation of pain.

5. Conclusions

5.1. Emotional self-regulation

Taken together, the results of the neuroimaging studies of emotional self-regulation reviewed in this article clearly show that the conscious and voluntary use of metacognition and cognitive recontextualization selectively alters the way the brain processes and reacts to emotional stimuli. This conclusion is particularly well supported by the Ochsner et al. (2004) study. In this study, the amygdala activity associated with the visual processing of negative IAPS pictures was up- and down-regulated in agreement with the regulatory goal.

Based on the results of these neuroimaging studies, we have previously proposed (Beauregard et al., 2004) a model according to which a few areas of the PFC participate in the neural mediation of the various top-down processes underlying emotional self-regulation. In our model the LPFC (BA 9, 10) is implicated in the selection of the appropriate cognitive operations in order to produce the desired outcome (e.g., down-regulation of the emotional response induced by film excerpts). To accomplish that role, the LPFC sends an executive command to the OFC (BA 11), which is involved in the modulation of the various aspects associated with emotion (e.g., physiological, feeling). In turn the OFC sends a message to the amygdala, which is led to reframe the interpretation of the emotional significance of the stimuli presented. The OFC is informed about this cognitive ''reframing'' by virtue of the anatomic projections that the amygdala sends back to this cortical region. The OFC also orders the rostral-ventral ACC (BA 24, 32) to modulate activity in brain structures involved in autonomic, visceral, and endocrine functioning (e.g., hypothalamus, insula, midbrain, brainstem nuclei). The rostral-ventral ACC conveys information related to the physiological state of the organism back to the OFC. Moreover, the OFC informs the MPFC (BA 10), which is involved in emotional self-consciousness, of the diverse changes related to the individual's feeling state. Our model further postulates that the awareness of the emotional state plays a crucial role in its regulation.

It is paramount to specify here that in this model, it is the whole person who consciously and voluntarily chooses to self-regulate emotion. In other words, the neural systems supporting the regulation of emotion are self-guided.

5.2. Psychotherapy

Etkin et al. (2005) have proposed that psychotherapy is a form of controlled learning that takes place in the context of a therapeutic relationship. Along the same lines, Kandel has hypothesized that psychotherapy can lead to long-term changes in behavior through learning. This type of learning would be supported by changes in gene expression that modify the strength of synaptic connections and structural changes that modify the anatomical pattern of interconnections between neurons (Kandel, 1998). In our view, many mental functions (including learning) are involved in psychotherapy. As a matter of fact, various forms of psychotherapy (e.g., behavioral,

cognitive, and psychodynamic) represent interventions based on different levels of the psychological organization (Cohen et al., 1997). Cognitive psychotherapy, for instance, focuses on negative cognitions (e.g., thoughts, beliefs, thinking patterns, schemata) that account for the development and maintenance of the psychopathological state (Beck and Friedman, 1990). In this form of therapy, the patient is taught to consciously recognize these negative cognitions and voluntarily modify them. As for psychodynamic psychotherapy, this type of treatment has its central focus on the set of expectations about self and others that organizes related affect, thought, and behavior (Fast et al., 1996). In the case of behavioral psychotherapy, the focus is mainly on dysfunction in simple forms of operant and associative conditioning (Foa et al., 1985). Given these fundamental differences, it is likely that the neuroplastic changes (at neural circuit, cellular, and molecular levels) associated with these various forms of psychotherapy differ.

Some of the neuroimaging studies on psychotherapy effects suffer from methodological limitations. Moreover, heterogeneities across these studies preclude a direct comparison between them. These heterogeneities concern the form of psychopathology examined (e.g., OCD, unipolar MDD, spider phobia), the neuroimaging techniques used (these techniques differ with regard to the phenomena measured, their sensitivity, etc.), the type of psychotherapy utilized (e.g., CBT, IPT), the therapists implicated, the methods used to analyze data, the sample size and type of control volunteers (healthy, waitlist), the condition of data acquisition (resting state, activation task), and the point of the second scan within the treatment course (Goldapple et al., 2004; Linden, 2006; Roffman et al., 2005). In addition, these studies do not allow determining whether the brain changes measured after psychotherapy are the cause or the effect of symptom reduction (Linden, 2006).

The goal of psychotherapy is to help people choose new patterns of behavior. The neural underpinnings of the psychotherapeutic process cannot be adequately studied and understood if a number of essential human features are not considered. These features include intentionality, consciousness, and mental causation (Lewis, 1994). Intentionality (the first-person perspective) is essential because the psychotherapeutic work is guided to a large extent by the content of patients' mental states and processes (e.g., thoughts and feelings). Consciousness is essential because psychotherapists have access to patients' inner world primarily though introspection. Obviously, mental causation is also an essential ingredient of therapeutic success (Lewis, 1994).

Despite the methodological limitations and heterogeneities of the neuroimaging studies of psychotherapy, it seems reasonable to assume that the results of these studies support the view that the mental functions and processes involved in the various types of psychotherapy exert a significant influence on the functioning and plasticity of the brain.

5.3. Placebo effect

The results of the neuroimaging studies of placebo confirm that the patient's beliefs and expectations play a pivotal role in this effect (Shapiro and Shapiro, 1997). These results also corroborate the notion that the placebo effect can be extremely specific. Thus, in PD patients a clinical placebo response can be associated with release of endogenous dopamine in the striatum (de la Fuente-Fernandez et al., 2001) or reduced activity in single neurons of the STN (Benedetti et al., 2004). As for MDD, placebo can produce metabolic changes in cortical and paralimbic brain regions that are relatively similar to those of fluoxetine (Mayberg et al., 2002). Furthermore, placebo manipulations can reduce neural activity in pain-responsive regions such as the rACC, anterior insula, and thalamus (Wager et al., 2004), and activate the endogenous opioid system in the DLPFC, pregenual rostral ACC, anterior insular cortex, and nucleus accumbens (Zubieta et al., 2005). Interestingly, in one of the experiments conducted by Wager et al. (2004), placebo-induced BOLD signal increases in DLPFC were correlated with placebo-induced BOLD signal reductions during pain in the thalamus, insula, and rACC. In addition, in the Zubieta et al. (2005), endogenous opioid activity in the DLPFC was significantly correlated with the magnitude of analgesia expected by the volunteers before placebo administration.

Taken together, the results of the neuroimaging studies of placebo effect demonstrate that beliefs and expectations can markedly modulate neurophysiological and neurochemical activity in brain regions involved in perception, movement, pain, and various aspects of emotion processing.

5.4. The Psychoneural Translation Hypothesis

The results of the neuroimaging studies reviewed here call in question the psychophysical identity theory and epiphenomenalism. For the psychophysical identity theory, mental processes (including intentional ones) are identical with neural processes (Feigl, 1958). For epiphenomenalism, mental processes are causally inert *epiphenomena* (side-effects or by-products) of neural processes. These findings also challenge eliminative materialism (or eliminativism). According to this view, mental processes and functions (e.g., consciousness, intentions, desires, beliefs, self) can be reduced entirely to brain processes. These mental processes and functions are pre-scientific concepts that belong to unsophisticated ideas of how the brain works (sometimes called ''folk psychology''). Eliminative materialism further proposes that all common language or ''folk psychology'' descriptions of mental experience should be eliminated and replaced by descriptions using neuroscientific language (Churchland, 1981). For these materialist views (psychophysical identity theory, epiphenomenalism, eliminative materialism), physically describable brain mechanisms represent the core and final explanatory vehicle for every kind of psychologically described data. These views are extremely counter-intuitive since our most basic experience teaches us that our choice of perspective about how we apprehend our mental states makes a huge difference in how we respond to them (Schwartz et al., 2005). With regard to this issue, we agree with Glannon (2002) that the tendency of modern neuroscience and biological psychiatry toward neurobiological reductionism, i.e., the reduction of persons to their brains (a form of ''neural

anthropomorphism''), is ill-advised and socially hazardous. We must keep in mind that the whole human person, not merely a part of a brain, thinks, feels, or believes. Indeed, the human person cannot be reduced to neural processes and it is difficult to understand a whole person without understanding the socio-cultural context in which the person lives.

Mind and brain are integrated and interdependent (Lewis, 1994). Nevertheless, the findings of the neuroimaging studies reviewed in this article strongly suggest that mentalistic variables (e.g., consciousness, metacognition, volition, beliefs, hopes) and their intentional content (the first-person perspective) are neither identical with nor reducible to brain processes (e.g., propagation of a nerve impulse, vesicular liberation of a neurotransmitter) (the third-person perspective). Regarding this issue, Bandura (2001) rightly points out that mapping the activity of the neural circuit underlying Martin Luther King's ''I Have a Dream'' speech would reveal little about the socially powerful significance of this speech and the agentic effort that invigorated its creation. The findings of the studies examined here also suggest that mental processes/events do exert a causal influence on brain plasticity and the various levels of brain functioning (e.g., molecular, cellular, neural circuit). Indeed, by changing our mind we are changing our brain (Paquette et al., 2003). Therefore, mental variables have to be considered as much as neurophysiological variables to reach an adequate understanding of the neural underpinnings of human behavior. The high explanatory and predictive value of agentic factors, such as beliefs, goals, aspirations, desires, and expectations (Bandura, 2001), cogently supports the interactionist view that the contents of subjective experience can causally influence physiological processes/events in the brain.

The most widely held objection to interactionism is that it is not compatible with the causal closure of the physical world. This metaphysical assumption implies that mind cannot exert any causal influence on the physical world (Chalmers, 2003). Yet, orthodox quantum theory is supportive of interactionism. For instance, in the von Neumann interpretation of quantum physics, the whole physical world, which comprises the body and brain of the agent, is described in the mathematical language of quantum mechanics. In this formulation the phenomenal evidence coming from subjective reports is treated as data pertaining to the psychologically described component of the agent, whereas the data from objective measurements made upon that agent, are treated as conditions on the physically described component of the agent. The apparent causal connection manifested between the psychological and physical components is explained by the causal connections between these components that are specified by the quantum laws (Schwartz et al., 2005).

To interpret these results of all the neuroimaging studies reviewed in this article, we need a hypothesis that accounts for the relationship between mental activity and brain activity. The *Psychoneural Translation Hypothesis* (or PTH) is such a hypothesis. It posits that the mind (the psychological world, the first-person perspective) and the brain (which is part of the ''physical'' world, the third-person perspective) represent two epistemologically and ontologically distinct domains that can interact because they are complementary aspects of the same underlying reality. According to the PTH, mind (including consciousness) represents an irreducible and fundamental aspect of our world. Furthermore, the PTH postulates that conscious and unconscious mental processes/events, which are neurally grounded, are selectively translated, based on a specific code, into neural processes/events at the various levels of brain organization (biophysical, molecular, chemical, neural circuits). In turn, the resulting neural processes/events are translated into processes and events in other physiological systems, such as the immune or endocrine system (the communication between the mind, the brain, and the other physiological systems constitute a *psychosomatic network*). Metaphorically, we could say that *mentalese* (the language of the mind) is translated into *neuronese* (the language of the brain). For example, fearful thoughts increase the secretion of adrenaline, but happy thoughts increase the secretion of endorphins. This informational transduction mechanism, which has emerged throughout the evolution of the human species, allows mental processes to causally influence brain activity in a specific manner.

With the emergence of self-consciousness, self-agency, and self-regulatory metacognitive capacities, evolution has enabled humans to consciously and voluntarily shape the functioning of their brains. These advanced capacities allow humans to be driven not only by survival and reproduction but also by complex sets of insights, goals, and beliefs. For instance, the ethical values associated with a given spiritual tradition help certain individuals to keep in check their emotional impulses and to behave in an altruistic fashion. In such cases, moral conscience replaces innate programming as behavioral regulator, and ethical behaviors constitute an emancipation from ''selfish'' genes and the primitive dictates of the mammalian brain. Such freedom is responsible for the fact that, despite the homogeneity of the human genome across human societies, we find fighting cultures that value and foster aggression whereas in pacific cultures, aggression is negatively perceived and almost non-existent (Alland, 1972; Sanday, 1981).

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