Title
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Permalink
https://escholarship.org/uc/item/3rj0s8db

Journal
Brain Structure and Function, 214(5)

ISSN
1863-2661

Authors
Paulus, Martin P.
Stein, Murray B.

Publication Date
2010-06-01

DOI
10.1007/s00429-010-0258-9

Peer reviewed

Brain Struct Funct (2010) 214:451–463
DOI 10.1007/s00429-010-0258-9

REVIEW

Interoception in anxiety and depression

Martin P. Paulus · Murray B. Stein

Received: 8 December 2009 / Accepted: 21 April 2010 / Published online: 21 May 2010

Abstract We review the literature on interoception as it relates to depression and anxiety, with a focus on belief, and alliesthesia. The connection between increased but noisy afferent interoceptive input, self-referential and belief-based states, and top-down modulation of poorly predictive signals is integrated into a neuroanatomical and processing model for depression and anxiety. The advantage of this conceptualization is the ability to specifically examine the interface between basic interoception, self-referential belief-based states, and enhanced top-down modulation to attenuate poor predictability. We conclude that depression and anxiety are not simply interoceptive disorders but are altered interoceptive states as a consequence of noisily amplified self-referential interoceptive predictive belief states.

Keywords Anxiety · Depression · Interoception · Insula · Belief · Alliesthesia

M. P. Paulus (✉) · M. B. Stein
Department of Psychiatry, University of California,
San Diego (UCSD), 8939 Villa La Jolla Drive,
La Jolla, CA 92037, USA
e-mail: mpaulus@ucsd.edu

M. P. Paulus · M. B. Stein
Department of Family and Preventive Medicine,
University of California, San Diego (UCSD), La Jolla, CA, USA

M. P. Paulus · M. B. Stein
Psychiatry Service, Veterans Affairs San Diego Health Care
System, San Diego, USA

Depression and anxiety

Depression is a common mental health condition that affects many aspects of daily life. Recent epidemiological data estimate the lifetime prevalence of major depressive disorder (MDD) at about 16% and the 12-month prevalence at 6% (Kessler et al. 2003). MDD is about twice as common in females relative to males (Kessler et al. 1993), manifests as an episodic but often recurrent illness with a mean duration of 16 weeks, and is comorbid with many other mental health conditions especially anxiety and alcohol use disorders. The current classification of depressive disorders (American Psychiatric Association 1994) is based on operational criteria that have been arrived at via consensus decisions by subject matter experts (Kendler and Gardner Jr. 1998). However, there is little evidence that these criteria delineate distinct biological entities or subsume similar biological conditions in one disorder (Sullivan et al. 1998). Nevertheless, there is substantial evidence from twin studies (Kendler et al. 1993), linkage studies (Hill et al. 1988), and association studies using single nucleotide polymorphisms (Liu et al. 2006) for strong genetic contribution to the susceptibility for depression. Other investigators have suggested that certain temperamental such as harm avoidance (Ongur et al. 2005) or personality traits such as neuroticism are associated with increased propensity to develop depressive disorders (Bienvenu et al. 2001). Neuropsychological investigations have revealed that an increased bias for remembering negative events (Watkins et al. 1996) and exaggerated response to negative feedback (Elliott et al. 1997) may constitute vulnerability factors for depression.

Anxiety disorders are the most common mental health problem (Kessler et al. 1994). These disorders comprise a heterogeneous group of conditions such as generalized anxiety disorder characterized by chronic worrying, panic disorder with a sudden onset of autonomic symptoms associated with a flooding of thoughts and anxious experiences, post-traumatic stress disorder characterized by intrusive recollections of exposure to extreme and potentially life-threatening events, obsessive compulsive disorder characterized by ruminative thinking and stereotyped actions aimed at relieving anxious thoughts, social phobia with fear of situations involving the potential for negative evaluation, and specific phobias with object-related anxiety symptoms. A common feature of all anxiety disorders is a profound avoidance of the event, object, or context, which has become associated with the experience or exacerbation of the anxiety symptoms.

Twin studies support the idea that anxiety disorders share a common genetic vulnerability that has been termed anxious-misery and fear (Kendler et al. 2003). For example, generalized anxiety disorder characterized by apprehensive expectation or chronic worry focused on multiple life situations (Barlow et al. 1986) is a chronic condition with a 12-month prevalence of approximately 3% that is commonly comorbid with MDD and associated with significant functional impairment (Stein 2004). Moreover, twin studies indicate that genetic and environmental risk factors for the anxiety disorders are similar between men and women and that the propensity for the development of anxiety falls into panic-generalized-agoraphobic anxiety versus specific phobias (Hettema et al. 2005). These studies, however, have also emphasized the individual environment experience as a contributing factor to the development of the disorder (Hettema et al. 2001). Neuropsychological studies have proposed that an increased emotional awareness (Novick-Kline et al. 2005), intolerance of uncertainty (Dugas et al. 1998), and a cognitive style termed looming vulnerability (Williams et al. 2005), i.e., mental representations of dynamically intensifying danger, appear to be among the cognitive predispositions to generalized anxiety disorder.

Interoception: the basis for “how I feel”

Interoception comprises sensing the physiological condition of the body (Craig 2002), as well as the representation of the internal state (Craig 2009) within the context of ongoing activities, and is closely associated with motivated action to homeostatically regulate the internal state (Craig 2007). Interoception includes a range of sensations such as pain (LaMotte et al. 1982), temperature (Craig and Bushnell 1994), itch (Schmelz et al. 1997), tickle (Lahuerta et al. 1990), sensual touch (Vallbo et al. 1995; Olausson et al. 2002), muscle tension (Light and Perl 2003), air hunger (Banzett et al. 2000), stomach discomfort related to low pH (Feinle 1998), and intestinal tension (Robinson et al. 2005), which together provide an integrated sense of the body’s physiological condition (Craig 2002). There are two pathways from the periphery to the insular cortex. First, these sensations travel via small diameter primary afferent fibers, which are thought to comprise a cohesive system for homeostatic afferent activity that parallels the efferent sympathetic nervous system (Craig 2007), and terminate on projection neurons in the most superficial layer of the spinal dorsal horn. The modality-selective lamina I spinothalamic neurons project to a specific thalamo-cortical relay nucleus, which in turn projects to a discrete portion of dorsal posterior insular cortex. Second, afferents traveling with the vagal and glossopharyngeal nerve synapse at the nucleus of the solitary tract (van der Kooy et al. 1984), which projects indirectly via ventroposterior thalamic nucleus and bi-directionally directly to the posterior insula (Shipley 1982). Moreover, the insular cortex projects directly to the specific “gastric” part of the dorsal vagal complex (Bagaev and Aleksandrov 2006) as well as other brainstem autonomic nuclei (Ruggiero et al. 1987). Studies in the rat have shown that the insular cortex is an important part of a highly interconnected central autonomic system, which may be organized in a viscerotopic manner (Saper 1982).

The posterior insula provides topographic and modality-specific interoceptive signals to the anterior insular cortex for integration (Craig 2003). These topographically organized and modality-specific pathways that carry interoceptive signals are integrated in the anterior insula cortex (Craig 2003), which is integrally connected with subcortical (Chikama et al. 1997), limbic (Reynolds and Zahm 2005), and executive control brain systems (for review, see Augustine 1985, 1996). An organism’s interoceptive state and hedonic state are integrated via reciprocal connections of the anterior insular cortex to corticolimbic and striatal reward circuit components such as (a) anterior cingulate (Augustine 1996), which is important for error processing (Critchley et al. 2005; Carter et al. 1998) and evaluation of action selection (Rushworth and Behrens 2008; Goldstein et al. 2007), to (b) amygdala (Augustine 1985; Jasmin et al. 2004; Reynolds and Zahm 2005; Jasmin et al. 2003), which is critical for processing stimulus salience (Paton et al. 2006), (c) nucleus accumbens (Reynolds and Zahm 2005), which processes the incentive motivational aspects of rewarding stimuli (Robinson and Berridge 2008), and (d) orbitofrontal cortex (Ongur and Price 2000b), which has been implicated in context-dependent evaluation of environmental stimuli (O’Doherty et al. 2001; Rolls 2004a, b; Bechara et al. 2000; Schoenbaum et al. 2003, 2006; Kringelbach 2005; Rolls and Grabenhorst 2008).

Thus, the anterior insula has access to a multi-dimensional representation and integration of the current and possibly anticipated (Paulus and Stein 2006) *feeling state* and is important for the capacity to be aware (Craig 2002; Critchley et al. 2004) of oneself, others, and the environment (Craig 2009). The columnar organization of the insular cortex shows a highly organized anterior-inferior to posterior-superior gradient (for example, see Mesulam and Mufson 1982), similar to other parts of the brain where cortical representations are based on modulatory or selective feedback circuits (Shipp 2005). Therefore, it is not surprising that anterior insula is involved in a wide range of processes, including pain (Tracey et al. 2000), interoceptive (Critchley et al. 2004), emotion-related (Phan et al. 2002), cognitive (Huettel et al. 2004), and social functions (Eisenberger et al. 2003). In summary, the anterior insula is important for subjective feeling states (Craig 2002; Critchley et al. 2004), and takes part in modulatory control of decision-making by interacting with other limbic, and cortical areas (Garavan et al. 1999).

Self: depression and anxiety

An important aspect of both anxiety and depression is the altered experience of the individual with respect to self, others and the future. Altered self-related processing, e.g., reduced tendency to self-favoring (de Jong 2002) and/or exaggerated negative self-image (Hirsch et al. 2003), has been implicated in the development of anxiety in general (Bruch et al. 1995) and social anxiety in particular (Clark and McManus 2002). Moreover, the anticipation of future harm to the self has been proposed as a key process in anxiety (Reiss 1997). Similarly, low self-esteem has been found using rigorous statistical methodology as a critical pathway for the development of depression (Kendler et al. 2006). This negative evaluative bias for self-relevant information persists even when overt symptoms of depression are absent (Gemar et al. 2001). Beck (1967) proposed that depression is a manifestation of an unrealistic negative view about the relationship between the self and the world.

An important aspect of self is corporeal awareness, which has been defined as the perception, knowledge and evaluation of one's own body as well as of other bodies (Berlucchi and Aglioti 2009). The meaning and implications of the concept of a "self" has been the focus of study for many philosophers and psychologists (James 1961). More recently, other disciplines such as psychiatry, neurology and neuroscience have begun to examine the psychological and biological basis for the existence of the "self" (Gusnard 2005). Reflecting upon oneself relates to an individual's self-concept and plays a crucial role in the maintenance of emotional and physical equilibrium. Being aware of our internal state modulates approach and distancing behaviors which, in turn, help us maintain and regain homeostasis (i.e., regulation of internal body state).

The neuroanatomy of self-relevant processing has recently been linked to the anterior cingulate cortex and surrounding midline cortical structures. Evaluative judgment produced significant activation in the anterior frontomedian cortex (Zysset et al. 2002). Others have reported that self-reassurance, i.e., positive evaluation of one self, was associated with left temporal pole and insula activation (Longe et al. 2009). Results revealed that activity in medial prefrontal cortex (mPFC) predicted both subsequent memory performance and judgments of self-relevance (Macrae et al. 2004). The mPFC activates during self- and other-evaluation versus the baseline semantic positivity-evaluation condition (Schmitz et al. 2004). Processing of information relevant to self activated superior medial parietal areas in comparison to other, whereas other led to greater activation in inferior medial parietal and left lateral frontal areas than self (Seger et al. 2004). Moreover, the correct recognition of self-encoded personality traits engaged dorso-medial prefrontal cortex and lateral prefrontal regions, premotor cortex, parietal and occipital cortex, caudate and cerebellum (Fossati et al. 2004). Finally, the mPFC (Amodio and Frith 2006) is often found active during resting conditions when individuals presumably engage in internally directed attention, processing self-relevant thoughts (Kelley et al. 2002) and beliefs (Wicker et al. 2003). This area is also involved in cognitive control, i.e., coordinating thought and action in accordance with internal goals (Miller and Cohen 2001), and is part of the "default mode" network involved in self-regulation and monitoring of the internal milieu (Gusnard et al. 2001).

Considering the impact that our own self-concept has on the way we behave and interact with our surroundings, it is not surprising to find the mPFC involved not only in the judgment of one's emotional state (Ochsner et al. 2004) but also in self-reflection (Johnson et al. 2002). According to Damasio, the "core self" is the summation of extero- and interoceptive stimuli that form the experience of the self as one integrated entity (Damasio 1999, 2003). Interoception or self-perception of bodily signals is an important component for the preservation of homeostasis via adaptive attention allocation, contextual evaluation, and action planning. The insula, considered the interoceptive center of the brain, is critical for evaluating the potential impact of stimuli on the body (Paulus and Stein 2006). Along with the mPFC, the insula plays a crucial role in the detection of emotionally salient stimuli (Morris et al. 1998; Phillips et al. 1998), as well as in the generation and regulation of affective responses (Phillips et al. 2003). Anatomically, the insular cortex shares afferent and efferent connections with the mPFC cortex (Ongur and Price 2000a) as well as the anterior cingulate gyrus (Reynolds and Zahm 2005).

Thus, in understanding the dysfunctions of interoception in anxiety and depression, one has to consider how interoceptive afferents and processes within the insular cortex are integrated with the neural representation of the self. In particular, because the self is a manifestation of past and present cognitive, affective and body state experiences, there must be a critical link between interoceptive processes and so-called dysfunctional schemas, i.e., organized elements of past reactions and experience that form a relatively cohesive and persistent representation, which guides perception and appraisals (Segal 1988). Belief-related processes provide this important link between the self and interoception.

Belief: a key dysfunctional process in depression and anxiety

Belief can be defined as a propositional mental construct that affirms or denies the truth of a state of affairs and is closely linked to basic judgment processes (Harris et al. 2007). The maintenance of a large and stable set of beliefs is essential for intelligent behavior, since this forms the basis for any actions which one may take to achieve one's goals (Elliott et al. 1995). More importantly, beliefs are frequently used to build mental models of the state of the world and are therefore important constructs to guide decision-making. The psychological approach to characterizing beliefs is complex and has focused recently on developing testable process theories, which can be disambiguated using modern neuroscience. To understand recent neuroscience findings of belief-based decision-making, it is important to briefly review a few relevant constructs.

The theory-of-mind and mentalizing has been an important construct for the conceptualization of beliefs. Theory-of-mind refers to the everyday ability to attribute independent mental states of self and others to predict and explain behavior (Happe 2003). The mechanisms underlying theory-of-mind have been extensively investigated via reasoning tasks that require participants to predict the action of agents based on information about beliefs and desires. Others have investigated the ability to explain the action of others and found systematic reasoning errors (Wertz and German 2007). Typically, we infer other people's beliefs from what they tell us. However, behavioral experiments have the advantage that the experimenter does not have to rely on the degree to which an individual is reporting truthfully. Behavioral experiments show that false beliefs engage greater cognitive resources resulting in longer response times, which may be due to the fact that subsequent judgments and decision-making need to take into account false beliefs as a conflict with the individual's perception of reality (Apperly et al. 2008).

Several neural substrates have been found to underlie belief-related processes. First, the temporo-parietal junction (TPJ) has been implicated not only in processing the attribution of beliefs to other people but also in the redirection of attention to task-relevant stimuli. Recent studies support the notion that the overlap between theory-of-mind and attentional reorienting suggests the need for new accounts of right TPJ function that integrate across these disparate task comparisons (Mitchell 2008). Others have found that the right TPJ differentially activated as a function of belief and outcome and was highest for cases of possible negative outcome based on the belief that action of a protagonist would cause harm to others, even though the harm did not occur (Young et al. 2007). In comparison to neuroimaging studies, a report of brain-damaged individuals revealed that, in addition to frontal cortex, left TPJ is necessary for reasoning about the beliefs of others (Samson et al. 2004). A study examining the contribution of mPFC and TPJ in false versus true belief reasoning showed that the dorsal part of the anterior cingulate cortex, the right lateral rostral prefrontal cortex and the right TPJ associated with false belief. The authors suggest that cognitive control areas are involved in action monitoring and stimulus-independent cognitive processing whereas the activation of the TPJ might be related to the computation of mental representations that create perspective differences, such as a person's false belief that contrasts with reality and therefore might be centrally involved in the decoupling mechanism (Sommer et al. 2007). Taken together, the TPJ appears to be crucial for the representation of a mental state associated with belief formation, possibly focused on disambiguating true from false beliefs.

The mPFC as pointed out above is often found to be active during "resting" conditions when individuals presumably engage in internally directed attention processing self-relevant (Kelley et al. 2002) thoughts and beliefs (Wicker et al. 2003). Some investigators have found that whereas mPFC is recruited for processing belief valence, TPJ and precuneus are recruited for processing beliefs in moral judgment mediating both encoding beliefs and integrating beliefs with outcome for moral judgment (Young and Saxe 2008). These findings are consistent with those of others showing greater activation of anteromedial prefrontal cortex and rostral anterior cingulate while participants implicitly made associations consistent with gender and racial biases. In contrast, associations incongruent with stereotypes recruited dorsolateral prefrontal cortex (Knutson et al. 2007).

Several studies have shown that direct appraisals of the self as compared to others more strongly recruited mPFC and right rostrolateral prefrontal cortex. Moreover, direct appraisals as compared to reflected appraisals recruited regions associated with a first-person perspective, e.g., posterior cingulate, whereas reflected as compared to direct appraisals recruited regions associated with emotion and memory, e.g., insula, orbitofrontal, and temporal cortex (Ochsner et al. 2005). Using event-related potential studies investigating the neural substrates of false belief reasoning revealed a specific late negative component which could be located in the middle cingulate cortex, which may be related to conflict or error detection (Wang et al. 2008). Another approach is to examine individuals suffering from dysfunctional belief systems. For example, individuals with delusions or fixed false beliefs provide an important clinical sample to examine the rigidity to which false beliefs are held. In comparison, subjects with delusions show significantly less rostral-ventral anterior cingulate activation but increased posterior cingulate activation during the determining of self-relevance, which may contribute to persecutory belief formation and maintenance (Blackwood et al. 2004). Taken together, the mPFC appears to be important for processing the degree to which beliefs are self-relevant, possibly with emphasis on the correct or incorrect, or acceptable versus unacceptable valence of the belief.

The strength to which one holds to a belief is an important regulator of human behavior and emotion. A recent neuroimaging study shows that states of belief, disbelief, and uncertainty differentially activated distinct regions of the prefrontal and parietal cortices, as well as the basal ganglia. These investigators propose that the final acceptance of a statement as “true” or its rejection as “false” relies on more primitive, hedonic processing in the mPFC and the anterior insula (Harris et al. 2007). Contrasting belief-based versus belief-neutral reasoning, some researchers have reported left temporal lobe versus parietal lobe activation, respectively, which is thought to be modulated by lateral prefrontal cortex in case of overcoming belief bias and ventral medial prefrontal cortex when succumbing to belief bias (Goel and Dolan 2003). Examining belief-based decision-making in a navigation task under uncertain conditions showed distinct regions of prefrontal cortex activation which was consistent with an underlying Bayesian model of decision-making that permits efficient goal-oriented navigation (Yoshida and Ishii 2006). Thus, dorsolateral and ventromedial prefrontal cortex may have important regulatory functions in moderating belief intensity and the degree to which beliefs influence decision-making. In comparison, when the observers judged the actions to reflect a false belief, there was activation in the superior temporal sulcus, orbitofrontal, paracingulate cortex and cerebellum (Grezes et al. 2004). Others have related belief-based decision-making to altruistic behavior and found that medial orbitofrontal-subgenual and lateral orbitofrontal areas mediate decisions to donate or to oppose societal causes whereas more anterior sectors of the prefrontal cortex are distinctively recruited when altruistic choices prevail over selfish material interests (Moll et al. 2006). Therefore, additional brain regions may modulate belief-based processing by contributing resources to (1) over-ride beliefs or (2) enforce beliefs, (3) engage in reward-related processing associated with beliefs (i.e., how good it feels to be right), or (4) determine how one’s own belief-based decision affects others.

Thus, altered interoceptive processing and anxiety or depression is closely linked to the view of the self, which—in turn—critically depends on belief-based processes. Before integrating these findings into a interoceptive mode of these disorders, however, one needs to consider that evaluative processes are not static and absolute but are dynamic and relative to the current internal state of the individual. In other words, body state-related information that affects the self and is being evaluated relative to one’s belief about oneself is subject to the momentary internal state of the individual. Alliesthesia is an important construct that links these processes together.

Alliesthesia: a process connecting the inside world to the outside world in depression and anxiety

Alliesthesia is a physiological construct introduced in 1973 to connect the stimulations that come from the “milieu exterieur” and affect the “milieu interieur” (Cabanac 1971). Alliesthesia critically links the subjective experience of external stimuli to the internal state of the individual. Cabanac (1971) proposed that a given external stimulus can be perceived as either pleasant or unpleasant, depending upon interoceptive signals. In particular, *negative alliesthesia* refers to the notion that repeated administration of a stimulus will affect the internal milieu in such a way that the valence of the stimulus is attenuated, e.g., the second or third stimulation by a painful stimulus is not experienced as aversely. In contrast, *positive alliesthesia* is observed if the repeated administration of a stimulus changes the internal milieu in such a way as to increase its valence. The constructs of negative and positive alliesthesia add the relative body state of the individual to the notion of habituation or sensitization. The relative body state has a profound effect on the experienced intensity and valence of the stimulus. Evidence for positive alliesthesia in anxiety comes from studies with socially anxious individuals. For example, repeated exposure to a social stressor resulted in a significantly greater increase of the skin conductance in a high anxious group relative to a comparison group (Eckman and Shean 1997). Moreover, individuals with higher trait anxiety showed less habituation during a repeated affective go/no-go paradigm (Hare et al.

2008). And some have argued that differential habituation may contribute to differences in self-reported anxiety (Houtveen et al. 2001).

Based on the alliesthesia construct, investigators have proposed a dynamic, homeostatic hypothesis of mood regulation (Cabanac et al. 2002; Ramirez and Cabanac 2003). This hypothesis proposes that (1) we experience the intensity of a positively valenced stimulus based on the evaluation of the stimulus relative to our internal state (Cabanac 1992), and (2) we engage regulatory mechanisms to maximize the hedonic aspect of the internal state. The alliesthesia construct can be applied to both rewarding and aversive stimuli, but it also provides an explicit connection between the internal state (i.e., interoception) and rewarding or aversive stimuli in the environment. As pointed out above, the construct of positive and negative alliesthesia is similar to the notion of sensitization and habituation. However, the latter constructs do not necessarily take into account the internal state of the individual and focus instead on an increase or decrease of frequency or intensity of an observable behavior. Thus, alliesthesia provides a direct link between the outer world and the inner world. Moreover, the reference to an internal state identifies additional circuitry, e.g., insular cortex and its connectivity to frontal cortical and extended amygdala circuits, which can be empirically tested for its role in processing appetitive or aversive stimuli.

Evidence for altered insula-related processing in depression and anxiety

Both depression and anxiety are multifactorial disorders that involve different brain processes and neural substrates. Here, we selectively review neuroimaging studies that provide evidence for the contribution of the insular cortex to the regulation and dysfunction of mood and anxiety. The results from these studies will be used to conceptualize the basic dysfunction in depression and anxiety as that of *alliesthesia of internal body signals due to altered belief-based self-relevance*. In other words, a change in the internal state of the individual, which may be due to an increased bias toward negative self-view (depression) or increased attentional biases toward threat (anxiety), sets up beliefs that are used to interpret afferent internal body signals. Moreover, external cues or internal thought processes generate an anticipation of aversive body states that sets up a body prediction error, i.e., the difference between the current and anticipated body state. This body prediction error acts as a motivating signal for individuals to withdraw (depression) or avoid (anxiety). There are several neuroimaging studies that provide evidence for an altered activation pattern of neural substrates that are important for interoceptive processing. For example, whereas increased self-criticism was associated with activity in lateral prefrontal cortex regions as well as anterior cingulate, self-reassurance was associated with—among other areas—increased insula activation. Moreover, lateral prefrontal cortex activity was positively correlated with high levels of self-criticism (Longe et al. 2009). Worrying, a set of self-relevant stereotypic cognitions, relative to neutral statements has been associated with increased brain activation in prefrontal cortex, striatum, and insula (Hoehn-Saric et al. 2004). Self-relevant aversive affective processing such as guilt was also found to involve left anterior insular cortex (Shin et al. 2000). Finally, sad self-relevant autobiographical memories were found to activate the ventral insula (Liotti et al. 2000). These examples provide clear evidence for the involvement of insular cortex during aversively valenced self-relevant processing.

The periacquaductal grey, amygdala, anterior cingulate cortex, and anterior insula are key neural substrates in pain processing (Ochsner et al. 2008; Wiech and Tracey 2009; Chua et al. 1999). However, aside from the direct experiencing of an aversive stimulus, the anticipation of aversive events and the interpretation of these events with respect to the construct of one self are important processes to consider in depression and anxiety. A number of studies have shown that the anticipation of aversive events involves the insular cortex. Several studies found that brain areas activated by anticipation of aversive pictures include dorsal amygdala, anterior insula, dorsal anterior cingulate cortex, right dorsolateral prefrontal cortex, and right posterior orbitofrontal cortex (Nitschke et al. 2006; Simmons et al. 2004). This network of activation in relation to the anticipation of aversive stimuli extends to other modalities such as monetary losses (Samanez-Larkin et al. 2008), conditioned stimulus predicting an aversive stimulus (Marschner et al. 2008), and the expectation of pain (Ploghaus et al. 1999). Moreover, insula activation is an important processing area for the affective elements to an individual's pain experience in subjects with depression (Giesecke et al. 2005). Some have argued that the insula and anterior cingulate are relatively more sensitive to the expectation of unpleasant stimuli relative to expecting pleasant or neutral stimuli (Herwig et al. 2007). Finally, uncertainty or ambiguity is an important aspect of anticipatory processing. Thus, it is not surprising that the degree to which an individual is sensitive to uncertainty correlates positively with activation in bilateral insula during affective ambiguity (Simmons et al. 2008). Others have reported that unpredictable stimulus presentations were correlated to brain activity in the anterior insula (Carlsson et al. 2006). Taken together, these data suggest that the insula plays an important role in processing the anticipation and subjective experience of aversive stimuli across a number of different modalities.

Another approach to identify brain processing differences is to examine the neural substrate activation differences in individuals that differ on their level of depression or anxiety. There is converging evidence from these kinds of studies that the insula plays a central role in anxiety and depression (Phan et al. 2002). Specifically, responding to sad mood distractors was found to be related to activation in anterior cingulate, ventromedial and orbital prefrontal cortex and insula (Wang et al. 2006). Increased sadness induced greater blood flow in subgenual cingulate and anterior insula (Mayberg et al. 1999). Transient sadness was associated with significant loci of activation in the anterior temporal pole and the midbrain, bilaterally, as well as in the left amygdala, left insula, and right ventrolateral prefrontal cortex, which some have related to the degree of sadness (Levesque et al. 2003), the degree of insomnia (Perico et al. 2005), or to the degree of stress-related ACTH regulation (Ottowitz et al. 2004). Dysthymic individuals relative to comparison subjects show greater brain activation during negatively valenced images in amygdala, anterior cingulate and insula (Ravindran et al. 2009). Patients with MDD show an enhanced responsivity in insula, anterior cingulate, and amygdala to non-painful stimuli and an increased activation in the right amygdala during anticipation of pain which is associated with more self-perceived helplessness (Strigo et al. 2008). The insula was also more sensitive in MDD patients compared to controls when presented with emotional images (Mitterschiffthaler et al. 2003). Studies examining the role of the insula in anxiety find a similarly increased sensitivity. For example, symptom provocation in anxiety activates, among other structures, bilateral insular cortex (Rauch et al. 1997). Anxiety-prone relative to comparison subjects show greater bilateral amygdala and insula activation to emotional faces (Stein et al. 2007). These individuals also exhibit greater bilateral insula activation during the anticipation of emotionally valenced pictures (Simmons et al. 2006). The enhanced insular response is also found in patients with specific phobia (Wright et al. 2003). Moreover, panic disorder patients show relatively less inhibitory (GABAergic) receptors in the insula, which is correlated with severity of illness (Cameron et al. 2007). Finally, several studies have highlighted the role of increased insula activation during aversive, anxiety-related processes such as combat-relevant stimuli (Vermetten et al. 2007) or heat temperature (Geuze et al. 2007), in patients with post-traumatic stress disorder. Taken together, these studies show clear evidence for altered insular cortex activation during a variety of different processes that share in common three features. First, they involve a stimulus that is evaluated with respect to one's self; second, the stimulus is typically viewed as aversive; and third, these processes occur even if the actual stimulus is not yet being perceived but is being anticipated.

Depression and anxiety: alliesthesia of internal body signals and belief-based self-relevance

The basic model that is proposed here (Fig. 1) is an extension and refinement of the insular model of anxiety that we proposed earlier (Paulus and Stein 2006). We considered that anxiety is a result of an increased anticipatory response to the potential of aversive consequences, which manifests itself in enhanced anterior insular cortex processing. The main aim of this model was to incorporate interoceptive processing aspects into the conceptualization of anxiety. In the current formulation, we extend this model in three ways. First, we propose that beliefs, i.e., propositional statements that refer to the state of the individual, which are processed in the mPFC and TPJ, contribute

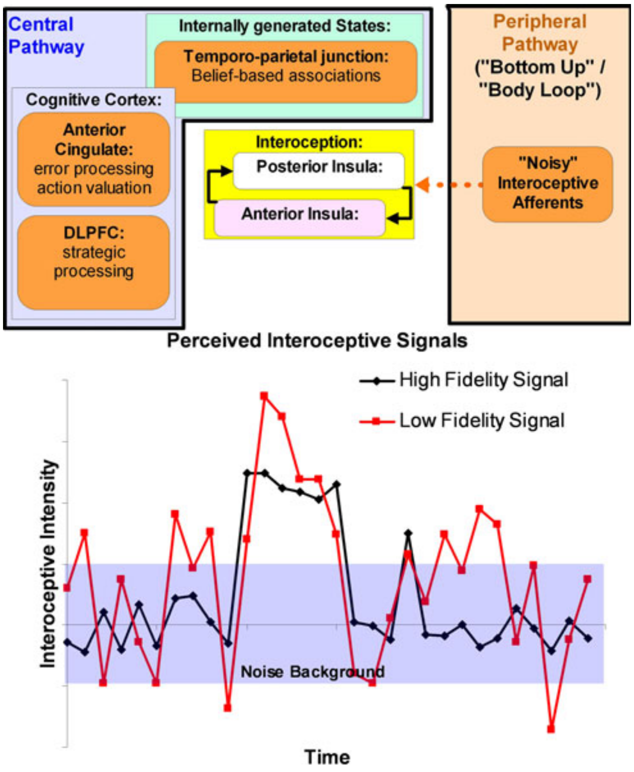

Fig. 1 Proposed alterations in brain circuitry (*top*) and the resulting process abnormalities in anxiety and depression. Briefly, "noisy" afferent interoceptive information results combined belief-based associations lead to an attempt of the cognitive control apparatus to differentiate predictive from non-predictive signals. The resulting experience (*bottom*) consists of amplified interoceptive afferents that are associated with carry poor differentiation of stimuli that carry predictive outcomes and create constant uncertainty for the future. More details are described in the text

significantly to the evaluation of the anticipatory interoceptive signals. Second, we assume that positive alliesthesia, i.e., an exaggeration of the valence (positive or negative) relative to the individual's internal state, plays a role in enhancing the aversive aspects of predictive body signals, i.e., initially sub-threshold afferent interoceptive signals are amplified and associated with the prediction of potential aversive or negative outcomes. Third, we propose that individuals at risk for anxiety and depression exhibit a reduced signal to noise ratio of interoceptive afferents. Specifically, when these individuals receive body signals, they cannot easily differentiate between those, which are associated with potential aversive (or pleasant) consequences versus those, which are part of constantly ongoing and fluctuating interceptive afferents. As a consequence of positive alliesthesia, these individuals imbue afferent interoceptive stimuli with motivational significance, i.e., an increased tendency to plan and act upon the reception of this input. Specifically, an internal body signal, e.g., a heart beat or inspiratory breathing sensation, is associated with negative valence and linked to belief-based processes, e.g., "there is something wrong with my heart" or "I am not getting enough air", which results in an increased "fight/flight" response and potential withdrawal or avoidance behaviors. As a consequence of this noisy amplification, top-down modulatory brain areas such as the anterior cingulate, dorsolateral prefrontal cortex, and orbitofrontal cortex are engaged constantly to differentially amplify or attenuate signals that are predictive or not predictive of future states, respectively. This relative "overactivity" of cognitive control-related brain areas is subjectively experienced as increased production of thoughts and associated beliefs, which provide prediction enhancing propositions. Practically, these cognitive processes result in "worrying", which is aimed at providing increased prediction accuracy.

The proposed model integrates a network of processes and neural processing substrates; however, it is less definitive about the causal chain of events. As proposed recently (Ochsner et al. 2009), distinct but overlapping neural substrates are involved in both top-down and bottom-up affective processes. Feeling states can be altered by both exaggerated valence of interoceptive afferents as well as exaggerated belief systems and it is not clear based on the current literature, which alteration is primary. It may even be possible to separate individuals into those who experience a predominant bottom-up dysregulation versus those who are subject to a primary top-down dysfunction. However, this will require the construction of careful experimental approaches that integrate interoceptive stimulation, belief states, and modulation of anticipatory states. The application of interoceptive modulation provides a unique experimental approach that takes advantage of the firm neuroanatomical basis of these processes to better probe self-related evaluative processes that are so critical for depression and anxiety.

There are two components of interoceptive dysregulation in anxiety and depression. First, we implicate specific neural substrates in the pathological processes observed in anxiety and depression. Specifically, consistent with our prior view of the role of insula in anxiety (Paulus and Stein 2006), this neural structure provides the contextualized body prediction error signal to other brain structures. The mPFC evaluates this body prediction signal based on self-relevant and belief-based processes. The dorsolateral prefrontal cortex and anterior cingulate respond to these contextualized self-relevant and belief-based signals to differentiate those that are predictive from those that are not. The relative increase in anterior cingulate activity has been reported in a number of studies with anxiety disorder individuals (McClure et al. 2007; Nitschke et al. 2009; Paulus et al. 2004). Therefore, altered brain processing in both depression and anxiety is thought to comprise the concerted and increased synchronicity of these brain structures with the ultimate goal of adapting the individual internal milieu to the demands of the outside world.

Second, the processes that are implicated in this model extend beyond interoception to include belief-based and self-referential aspects. In this context, one could consider the combination of contextualized interoceptive afferents, belief-based and self-referential constructs as "interoceptive prediction schemas" of the individuals. For example, a rapid heart rate may fit into a "positive excitement schema" or into an "anxious potentially harmful schema", i.e., the same afferent interoception can result in fundamentally different interpretation and therefore have completely different self-relevance. One important direction is to determine the degree to which these interoceptive prediction schemas evolve. In particular, one needs to consider the interplay between the disposition to experience a poorer signal to noise ratio of interoceptive afferents and specific experiences, which may result in greater uncertainty due to the catastrophic consequences of not predicting a significant aversive event. For example, an individual who is particularly sensitive to interoceptive afferents and is exposed to childhood mistreatment may need to engage all available top-down modulatory processes to differentiate interoceptive fluctuation from predicting an impending episode of mistreatment.

The proposed extension of the initial model is consistent with other conceptualizations of depression and anxiety. For example, altered self-schemas particularly as they relate to personal worth (Teasdale et al. 1995) have been proposed as a basic vulnerability for depression (Williams et al. 1990). Moreover, a mismatch between self-relevant schemas such as negative affectivity and physiological arousal has been observed in individuals with generalized anxiety disorder (Dibartolo et al. 1997). Practically, individuals with anxiety disorders show a marked tendency to underestimate their level of physical exertion (Vaitl 1996). Subjects with high emotional reactivity showed a higher degree of interoceptive awareness based on the heart beat detection task and higher trait anxiety, which has been taken to suggest that a chronically increased sympathetic outflow might be one variable contributing to the establishment of high interoceptive awareness (Pollatos et al. 2007a). Further analyses, however, revealed that the relationship between emotional arousal and trait anxiety was mediated by differences in interoceptive awareness (Pollatos et al. 2007b). Thus, there is some evidence that anxious individuals show increased interoceptive sensitivity, which may be associated with reduced interoceptive accuracy. Finally, enhanced fear-relevant schemas in the context of external stimuli have been proposed to contribute to the formation of excessive anxiety (Teachman et al. 2001).

The value of the current model is to dissect both processes and brain structures to be able to formulate and test novel hypotheses about the fundamental dysfunction in depression and anxiety. Specifically, we predict that individuals with anxiety and depression show (1) reduced ability to adequately report interoceptive afferents; (2) exaggerated response to aversive interoceptive afferents, even those that are not predictive of aversive outcomes. As a consequence, these individuals should perform more poorly on tasks that are guided by somatic signals, e.g., the Iowa gambling task. In summary, we propose that both depression and anxiety represent altered interoceptive states as a consequence of noisily amplified self-referential interoceptive predictive belief states. Due to the uncertain and noisy ascending interoceptive input, unstable interoceptive schemas are developed that foster predictive uncertainty and as a consequence an increased attempt to top-down control and predict these inputs.

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