An Insular View of Anxiety

Martin P. Paulus and Murray B. Stein

We propose a general hypothesis that integrates affective and cognitive processing with neuroanatomy to explain anxiety proneness. The premise is that individuals who are prone to anxiety show an altered interoceptive prediction signal, i.e., manifest augmented detection of the difference between the observed and expected body state. As a consequence, the increased prediction signal of a prospective aversive body state triggers an increase in anxious affect, worrisome thoughts and other avoidance behaviors. The anterior insula is proposed to play a key role in this process. Further testing of this model—which should include investigation of genetic and environmental influences—may lead to the development of novel treatments that attenuate this altered interoceptive prediction signal in patients with anxiety disorders.

This Neuroscience Perspectives article is divided into five parts. First we will explain the concept of interoception; second, we will review the notion of error signaling as a means of learning and prediction; third, we will assemble the neural processing model; fourth, we will present results from several studies as support for this model; fifth, future directions will be highlighted.

Interoception

Interoception can be defined as the sense of the physiological condition of the entire body (Craig 2002). Interoceptive information includes sensations such as temperature, pain, itch, tickle, sensual touch, muscular and visceral sensations, vasomotor flush, hunger, thirst, air hunger and others. Interoception has long been thought to be critical for self-awareness because it provides the link between cognitive and affective processes and the current body state. The neural system that underlies interoception can be conceptualized as a homeostatic neural system that conveys signals from small-diameter primary afferents and creates an internal representation of the entire body. In particular, ascending brain areas involved include the midbrain reticular nuclei, ventromedial and ventroposterior thalamus, and the interoceptive (posterior) insular cortex, which is integrated in the anterior insular cortex of the dominant (right) hemisphere (Craig 2002).

There are two important aspects of interoception. First, interoceptive sensations are often associated with intense affective and motivational components, e.g., thermal sensation of heat, although experienced in the tissue that is in contact with the object, is immediately attributed to the object and associated with a strong withdrawal action. Second, the evaluative component of the signal is highly dependent on the homeostatic state of the individual, e.g., the same degree of heat (or cold) can be motivationally rewarding or punishing depending on the individual’s core body temperature. The insular cortex has bidirectional connections to both the amygdala and to the nucleus accumbens (Reynolds and Zahm 2005) as well as the orbitofrontal cortex (Ongur and Price 2000). In the amygdala, neurons can rapidly adjust their activity to reflect both positive and negative value of an external stimulus, which is predictive of how fast monkeys learn to respond to a stimulus (Paton et al. 2006). Therefore, the insular cortex is centrally placed to receive information about the salience (both appetitive and aversive) and relative value of the stimulus environment and integrate this information with the effect that these stimuli may have on the body state.

The information about the interoceptive state processed in the anterior insula is relayed to the anterior cingulate cortex, which, as part of the central executive system, can generate an error signal that is critical for the allocation of attentional resources (Carter et al. 1999). Thus, interoception involves monitoring the sensations that are important for the integrity of the internal body state and connecting to systems that are important for allocating attention, evaluating context, and planning actions. The role of the insula is thus focused on how the value of stimuli might affect the body state. In contrast, the anterior cingulate is thought to compute an error signal between a predicted and observed outcome to indicate the need for deployment of attentional resources in order to adjust behavior or cognition (Botvinick et al. 2004).

Error processing, learning and prediction: An important evolutionary advantage associated with the development of complex cortical circuitry, which is able to provide top-down modulation of ascending sensorimotor information, is the ability to predict future states. This ability, in turn, is fundamentally related to learning associations between stimuli and future pleasant or aversive outcomes. For example, the rate of reward learning depends on the discrepancy between the actual occurrence of reward and the predicted occurrence of reward, the so-called ‘reward prediction error’ (Schultz et al 1997). The neural circuitry involving reward-related learning and anticipatory reward processing has been investigated intensely and is thought to involve the ventral striatum and orbitofrontal cortex. However, analogous processes involving aversive stimuli and the prediction of aversive outcomes have been less well investigated. Nevertheless, there is some indication that similar learning processes occur with aversive stimuli and that the insular cortex is critically involved in generating anticipatory signals that are important for learning about aversive outcomes (Ploghaus et al 1999). The anterior insular cortex, as part of the interoceptive system, may provide information about future aversive body states associated with conditional stimuli and signal this information to brain areas that are critical for the allocation of attention and the execution of actions.

The Anxious Phenome

Anxious individuals focus on the likelihood (or, as they sometimes perceive it, inevitability) of a future aversive bodily state in certain contexts. The cognitive-behavioral conceptualiza-

From the Departments of Psychiatry (MPP, MBS) and Family & Preventive Medicine (MBS), University of California, San Diego (UCSD), La Jolla, California; and the Psychiatry Services (MPP, MBS), Veterans Affairs San Diego Health Care System, La Jolla, California.

Address reprint requests to Murray B. Stein, M.D., M.P.H., Department of Psychiatry, UCSD, 8950 Villa La Jolla Drive, Suite B-218, La Jolla CA 92037; E-mail: mstein@ucsd.edu.

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tion of anxiety disorders is based on behavioral theories of fear conditioning and cognitive theories that highlight the role of anxious thinking (Clark 1986). In the cognitive-behavior literature, “anxiety sensitivity” is the construct used to describe the tendency of certain individuals to view interoceptive sensations as dangerous or threatening (Reiss et al 1986). We propose here that this tendency is mediated through a neural circuit that features a central role for the anterior insula, and that persons with high anxiety sensitivity perceive a heightened interoceptive prediction signal. Individuals with high anxiety sensitivity are prone to certain kinds of anxiety disorders (e.g., panic disorder). For example, it has been suggested that panic disorder develops because exposure to panic attacks causes the conditioning of anxiety to exteroceptive and interoceptive cues (Bouton et al 2001). Anxiety sensitivity has both heritable (Stein et al 1999) and developmental (e.g., childhood trauma) (Scher & Stein 2003) origins. By linking a specific neuroanatomy to constructs that are important for anxiety, it becomes possible to examine neural substrate specific hypotheses that involve the genetic and/or environmental precursors of neurotransmitter, second messenger, or intracellular signaling systems to an altered anticipatory prediction signal in the anterior insular cortex in individuals with high levels of anxiety.

**Altered Interoception and Anxiety**

An altered signal of an impending aversive body state provides the basic link between altered interoception and anxiety. The key hypothesis put forth in this review is that individuals who are prone to anxiety show an altered interoceptive prediction signal, i.e., they experience an augmented signaling of the difference between the observed and expected body state. This hypothesis is schematically outlined in Figure 1. A stimulus (house) predictive of an aversive outcome (injury by an angry male) initiates an aversive body state prediction (wavered image of various body organs), which is represented as a prediction signal in the anterior insular cortex. There are two possibilities of altered prediction signaling. First, anxiety-prone individuals may experience an attenuated baseline interoceptive state and a normal interoceptive expectation resulting in a larger error signal. Alternatively, anxiety-prone individuals may have a normal baseline interoceptive state but an exaggerated expected body state resulting in a larger error signal. Although there is little evidence for the first hypothesis, some evidence may support the second (Critchley et al 2004).

Moreover, we propose that altered interoception is the primary process underlying the initiation of an anxiety state and that the affective, cognitive and behavioral components are a consequence of this altered prediction signal. In particular, we propose that cognitive (e.g., worrying) and behavioral (e.g., avoidance) components associated with this altered prediction signal are attempts to bring alternative brain resources to bear in order to attenuate the difference between observed and expected body state. This is in line with other contemporary learning theories of anxiety, which combine an anxiety diathesis model with specific post-conditioning processes (for review see Mineka and Zinbarg 2006). For example, individuals who have a history of uncontrollable and unpredictable life stress may come to use worry about possible bad outcomes or dangerous events as a cognitive avoidance response. The suppression of emotional and interoceptive responses when people worry serves to reinforce the process of worry (avoidance) but also prevents extinction (Borkovec and Roemer 1995). The altered interoception hypothesis focuses on anterior insular cortex dysfunction as a key component of these processes, and complements previous studies of altered amygdala functioning (Rauch et al 2003) by emphasizing the functional connections of the insula with the amygdala (Charney 2003; Drevets 2003).

Though much recent research attention in anxiety disorders has focused on a key role of amygdala abnormalities, there are several reasons to consider the notion that pathological anxiety is etiologically related to insula function instead of (or in addition to) altered amygdala function. First, the anatomical connections between insular cortex and limbic and executive functioning areas place this brain structure at the center of altered homeostatic physiological sensations and increased cognitive engagement, consistent with the view that anxiety consists of two key components: sympathetic hyperarousal and worry. Second, the focus on an altered prediction signal is consistent with the view of anxiety as a future oriented cognitive and emotional characteristic. Third, the altered prediction signal generated by or modulated within the anterior insular cortex provides a process by which learning and conditioned associations assume a pivotal role in the development of pathological anxiety. Fourth, although the amygdala is critically involved in mediating anxiety, the complex and integrative nature of anxiety clearly points toward the involvement of a cortical structure that is capable of initiating and maintaining complex representations.

**Altered Insula Function and Anxiety**

Functional neuroimaging studies have linked insular cortex activation to (1) modulation of affective processing, e.g., processing of fearful faces, processing of facial expressions of disgust, anticipation of electric shocks, the degree of preference during ingestion of chocolate, and script induced sad mood; (2) cognitive and affective processes during learning, e.g., aversive Pavlovian conditioning or aversive trace conditioning, perceptual awareness of threat, penalty related activation, and error related brain activation; and (3) aversive interoceptive processing, e.g., synaesthesia, noxious heat or cold stimuli, coding of pain intensity, and expectation of painful stimuli. These, and other studies, show clearly that the insular cortex is important for linking emotions to cognitive processes and behavioral responses (e.g., see Nitschke et al. 2006).

There is evidence of altered insular functioning in patients with anxiety disorders. Symptom provocation in individuals with obsessive-compulsive disorder, simple phobia, or posttraumatic stress disorder has been shown to be associated with increased cerebral blood flow in bilateral insular cortex (Rauch et al 1997). Panic disorder patients show a dramatic down-regulation of GABA(A) receptors in the right insular cortex (Malizia et al 1998). Social phobia patients show differential blood flow reduction in the insular cortex during a public speaking task (Lorberbaum et al 2004). Individuals with specific phobia show an exaggerated right insular response to fearful faces (Wright et al 2003). Patients with generalized anxiety disorder (GAD) show a reduced activation in the insular cortex after symptom reduction by citalopram (Hoehn-Saric et al 2004). And insular activity has been linked with the contamination/washing symptom dimension of obsessive-compulsive disorder (OCD) (Mataix-Cols et al 2004). Thus, several avenues of research, albeit preliminary, point to altered insular function being a feature of many (if not all) of the anxiety disorders.

Several investigators have emphasized that the insular cortex may be central for our understanding of anxiety promenence. Specifically, Critchley and colleagues have suggested that the
insular cortex processes visceral responses accessible to awareness as subjective feeling states (Critchley et al 2004). We have shown that the degree of activation in right anterior insular cortex during risky decision-making is correlated with both harm avoidance and neuroticism, that anticipation of emotionally aversive stimuli activates right insular cortex (Paulus et al 2003), that anxiety-prone individuals have bilaterally increased insula activation during emotion processing (Stein et al 2006), and that lorazepam dose-dependently attenuates activation in bilateral anterior insula (Paulus et al 2005). Taken together, these observations strongly suggest that individuals prone to anxiety have heightened activity in the anterior insula during processing of certain kinds of salient stimuli, and further suggest the testable hypothesis that anxiolytic treatments share the ability to reduce insular activity as requisite for their therapeutic action. Finally, altered prediction signal processing in the insular cortex may, in part, be due to the enhanced signaling of saliency by the amygdala. Thus, future studies may need to further refine the proposed hypothesis to better delineate the contribution of different structures and their functional connectivity.

Clinical Implications for Understanding Symptoms

How does an individual respond to a heightened interoceptive prediction signal? Because individuals focus on the differ-
ence rather than on an absolute experience of a body state, we suggest that learning mechanisms similar to those described for dopamine-dependent temporal difference models (i.e., signal in anticipation of reward) are at work in maintaining the altered anxiety state (i.e., anticipation of feared stimulus). Specifically, we suggest that the enhanced difference signal drives the continued engagement of cognitive resources to “solve the problem,” which manifests as aimless, non-goal-directed cognitive activity that is experienced as generalized or anticipatory anxiety or worry. This notion is not unlike a recently proposed model for drug addiction, which poses that drugs of abuse create a residual prediction error, resulting in increased behavioral rigidity as a consequence of continued error signal feedback (Redish 2004). Cognitive avoidance (including worry) may serve as a form of “body disengagement” aimed at attenuating the experience of the difference between the observed and the expected body state. And, of course, individuals may develop and maintain extensive behavioral avoidance (“phobic avoidance”) with the same purpose in mind. The avoidance of stimuli that generate prediction signals is, because of the nature of the predicted aversive body state, in itself negatively reinforcing (Skinner 1966), e.g., animals will increase the frequency of a behavior that leads to the omission of an aversive event.

**Insular Cortex—Genes and Neurotransmitter Systems**

How is altered anterior insula functioning in anxiety mediated by molecular cell signaling cascades or neurotransmitter systems? Fear conditioning induces the expression of immediate-early genes in the basolateral amygdala, which probably trigger secondary transcriptional cascades to stabilize early synaptic changes. Early gene expression has been found in response to both exposure and re-exposure to unconditioned and conditioned stimuli in insular cortex (Chen et al 2004). Selective serotonin reuptake inhibitors and non-serotonergic antidepressants increase immediate-early gene expression in insular cortex. It is well known that painful stimuli activate the insular cortex and that pain modulation is mediated via GABAergic inhibition of glutamatergic stimulation in the locus coeruleus and basolateral amygdala. Substance P plays an important role in the insula of glutamatergic stimulation in the locus coeruleus and basolateral amygdala. Substance P has an important role in the insula during conditioned taste aversion. The central nucleus of the amygdala is involved in mediating fear and anxiety-related behavioral and modulates brain CRF activity (Kalin et al 2004). Others have proposed that interaction between CRF and serotonin in paralimbic areas is important for the expression of anxiety-like behaviors, consistent with the CRF1 receptor’s role in the acquisition of aversive experiences.

**Future Directions**

The general hypothesis that anxiety reflects a heightened interoceptive prediction signal processed in the anterior insular cortex will need to be elaborated and extended in future studies. There are several questions that need to be addressed: (1) Is this alteration similar across different anxiety disorders (e.g., panic disorder vs. GAD)? (2) What specific molecular systems mediate this altered prediction signal? (3) How do drug and psychological treatments for anxiety affect the prediction signal? (4) Is this process equally important for acquisition, maintenance, and extinction of conditioned stimuli predicting aversive body states? These are only a few of the questions that will need to be addressed to improve our understanding of the role of the anterior insular cortex in anxiety.
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