THE ROLE OF NEUROIMAGING FOR THE DIAGNOSIS AND TREATMENT OF ANXIETY DISORDERS

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Neuroimaging comprises a set of tools, which include different types of magnetic resonance imaging such as functional magnetic resonance imaging (fMRI), Magnetic Resonance Spectroscopy (MRS), Arterial Spin Labeling (ASL), and radiotracer imaging such as positron emission tomography and single photon emission computed tomography. The focus of this review is to address the question whether fMRI can contribute to the diagnosis and treatment of anxiety disorders. Key anxiety processes and neural substrates are reviewed. The main findings and shortcomings of fMRI in the context of anxiety are briefly summarized. Finally, the next stages of developing fMRI for diagnosis and treatment are highlighted. The main conclusion of this review is that fMRI could become a clinical tool for the diagnosis and treatment of anxiety disorders, but neuroimaging groups will need to better develop its specificity and sensitivity so that fMRI results can be meaningful for an individual patient not just for groups of individuals. Depression and Anxiety 25:348–356, 2008. © 2008 Wiley-Liss, Inc.

fMRI–WHAT IS IT AND WHAT DOES IT MEASURE?

Functional magnetic resonance imaging (fMRI) is a technique that enables one to map cognitive, affective, and experiential processes onto brain substrates. However, fMRI is not about increased or decreased activation in a certain part of the brain; rather it is a proxy measure about how complex cognitive, emotional, social, and other experiential processes are implemented in different neural systems. For example, it is important to realize that it makes little sense to talk about hyperactivity in the amygdala in individuals with anxiety disorder without referencing the process, which is being measured during the amygdala hyperactivity, i.e. the task that individuals are engaged in while the functional images are obtained. Although the human brain comprises only about 2% of the body mass, it accounts for approximately 20% of its total oxygen consumption [Shulman et al., 2002]. Deoxyhemoglobin has paramagnetic effects in the blood upon the nuclear magnetic resonance transverse relaxation times of nearby water protons in the tissue [Ogawa and Lee, 1990]. The fact that changes in the oxygen level in the blood can affect the fraction of hemoglobin in the deoxygenated state can be utilized as an image contrast and was termed as blood oxygenation level-dependent (BOLD) fMRI [Ogawa et al., 1990]. Recent BOLD fMRI experiments in the awake human visual cortex have shown that the ratio between BOLD--fMRI signal change and baseline signal is linearly proportional to the change in blood flow relative to the baseline blood flow [Hyder et al., 2001]. Moreover, increases in baseline blood flow is thought to be proportional to

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total deoxyhemoglobin within a voxel [Buxton et al., 2004]. For example, increased baseline cerebral blood flow (CBF) by breathing CO₂ reduces the BOLD response to the same task substantially [Kastrup et al., 1999]. Therefore, the BOLD signal reflects the effect of neural activity on dynamic changes in CBF, cerebral blood volume, and the cerebral rate of oxygen metabolism through a process generally referred to as neurovascular coupling. Thus, prior experimental and theoretical work suggests that a measure of baseline CBF in addition to fMRI could also be useful in determining the non-process-specific effects. Specifically, baseline CBF measures can be used as covariates in the interpretation of BOLD changes induced by anxiety treatments. In addition, group differences in both baseline CBF and the effect of anxiety treatments on CBF can be interpreted as additional independent factors in a bioassay. For example, if baseline CBF in amygdala is found to be higher in anxiety-prone subjects, it may turn out that the most promising anxiolytic drug candidates are those that reduce baseline CBF in amygdala to normal levels.

**NEURAL SYSTEMS RELEVANT FOR ANXIETY DISORDERS**

When conducting neuroimaging experiments in the field of anxiety disorders, one is concerned with four issues: (1) What is the process that one wants to measure; (2) what task one wants to use to assess the process; (3) how is brain activation related to the process at hand; and (4) how is this process altered in individuals with anxiety disorders. These issues are complex and there is no clear resolution as to the best processes, the best tasks, or the basic nature of dysfunctional processes in anxiety disorders. Instead, there are several approaches that researchers have taken to map out the functional circuitry of anxiety disorders. Moreover, the situation is complicated by the fact that studies with anxiety disorder subjects are frequently complicated by concomitant medication treatment or other non-anxiety comorbidity. Although, these results are relevant for “real-life” patients, they make it difficult to uniquely attribute dysfunctional processes to specific anxiety disorders. Clearly, the amygdala plays a critical role in the functional neurocircuitry of anxiety disorders. The amygdala is involved in normal fear conditioning and is implicated in the pathophysiology of several different anxiety disorders [Charney, 2003; Rauch et al., 2003]. However, this structure is also important for other emotional information processing and behavior [LeDoux, 1992]. Functional neuroimaging studies have shown amygdala activation in fear conditioning [Buchel et al., 1998], reward-related processing [Breiter and Rosen, 1999], encoding of emotionally salient information [Canli et al., 2000], risk-taking [Ernst et al., 2002], processing positively valenced stimuli [Garavan et al., 2001], and appetitive or aversive olfactory learning [Gottfried et al., 2002]. Individuals with social anxiety disorder [Stein et al., 2002] or posttraumatic stress disorder [Rauch et al., 2000] show amygdala hyperresponsivity to fearful or angry faces. In addition to the amygdala changes, panic disorder (PD) patients have decreased benzodiazepine receptor binding in left hippocampal and precuneus [Bremner et al., 2000] and in right orbitofrontal cortex and right insula [Malizia et al., 1998].

In addition to the amygdala, a network of structures, which includes the insula, anterior cingulate gyrus, and medial prefrontal cortex (MPFC), are important for the identification of the emotional significance of a stimulus, to generate an affective response, and to regulate the affective state [Phillips et al., 2003]. The insula [for review, see Augustine, 1985, 1996] is one of the paralimbic structures and constitutes the invaginated portion of the cerebral cortex, forming the base of the sylvian fissure. The insular cortex has been considered limbic sensory cortex by some investigators [Craig, 2003]. A central insular sulcus divides the insula into two portions, the anterior and posterior insula. The anterior insula is strongly connected to different parts of the frontal cortex, whereas the posterior insula is connected to both the parietal and temporal cortex [Ture et al., 1999]. The columnar organization of the insular cortex shows an highly organized anterior inferior to posterior superior gradient [for example, see Mesulam and Mufson, 1982]. Specifically, whereas posterior insular is characterized by a granular cortical architecture, the anterior inferior insula has an agranular columnar organization, i.e. lacks layer four granular cells. This type of transition is found in other parts of the brain whenever cortical re-representations are based on modulatory or selective feedback circuits [Shipp, 2005]. Finally, the discovery of spindle cells within the anterior insular–orbitofrontal transition region [Nimchinsky et al., 1999] has provided a cellular substrate underlying the possibility of widespread cortical integration. Insular cortex appears to be particularly important for subjective feeling states and interoceptive awareness [Craig, 2002; Critchley et al., 2004]. The insula has afferent and efferent connections to medial and orbitofrontal cortex, anterior cingulated, and several nuclei of the amygdala [Augustine, 1996]. Although insula activation has been frequently associated with disgust [Phillips et al., 1998], there is increasing evidence of a broader role for this brain structure in emotion processing [Phan et al., 2002]. Insula activation is thought to be involved in differential positive versus negative emotion processing [Buchel et al., 1998], in particular fearful face processing [Morris et al., 1998a], pain perception [Gelbar et al., 1999; Peyron et al., 2000], and when individuals were asked to make judgments about emotions [Gorno-Tempini et al., 2001].

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The MPFC, an area that includes various parts of the prefrontal cortex including the superior frontal gyrus, the para-cingulate, and the inferior frontal gyrus, in addition to the amygdala and insula has been recognized as increasingly important for the regulation of emotion in general and anxiety-related processing in particular. For example, the correct recognition of self-encoded personality traits engaged dorso-MPFC and lateral prefrontal regions, premotor cortex, parietal and occipital cortex, caudate and cerebellum [Fossati et al., 2004]. Other investigators have shown that activity in MPFC predicted both subsequent memory performance and judgments of self-relevance [Kelley et al., 2002; Macrae et al., 2004]. More specifically, individuals while making judgments about trait adjectives under three experimental conditions (self-relevance, other-relevance, or case judgment) show that the MPFC was selectively engaged during self-referential processing [Kelley et al., 2002], which is consistent with other findings that there is a common area of medial prefrontal activation during the “ME” conditions of self- and other-evaluation versus the baseline semantic positivity-evaluation condition [Schmitz et al., 2004]. Others have reported that self and other decisions both activated bilateral medial areas of the frontal and parietal lobes and the bilateral insula in comparison with a letter task [Seger et al., 2004]. These evaluative judgments are associated with activation in the anterior frontomedian cortex (BA 10/9), the inferior precuneus (BA 23/31), and the left inferior prefrontal cortex (BA 45/47). Some investigators have made a distinction between the anterior frontomedian cortex and in the inferior precuneus. Whereas the latter was found to be activated by episodic retrieval processes, supporting its function as a multimodal association area that integrates the different aspects of retrieved and newly presented information, the anterior frontomedian cortex was mainly involved in evaluative judgments, supporting its role in self-referential processes and in the self-initiation of cognitive processes [Zysset et al., 2002]. Activation in anterior insula and rostral ACC during “self” versus “other” judgments, suggests that the neural substrate for empathic experience not only involves self-relevant processing areas but partially engages the “pain matrix” [Singer et al., 2004]. Moreover, the nucleus accumbens responds to both increasing emotional intensity and self-relatedness. Finally, activity in the amygdala was specifically related to affective judgments and emotional intensity. The volitional act of appraising the extent of personal association specifically engaged the ventral MPFC, and additionally recruited dorsal medial frontal regions and insula as the extent of self-relatedness increased [Phan et al., 2004]. Taken together, MPFC regions may contribute to the neural instantiation of aspects of the multifaceted “self” [Gusnard et al., 2001]. Thus, amygdala, insula, and MPFC are critical for the recognition, anticipation, and expression of emotions as they relate to the self.

**EMOTIONAL PROCESSES RELEVANT FOR ANXIETY DISORDERS**

Emotional face processing has been the most often used behavioral paradigm to probe dysfunctional neural systems in anxiety disorder. However, to identify, recognize, and respond to facial emotional stimuli is a complex process. This involves a well-studied neural circuitry, which is altered in individuals with anxiety disorders. Adjacent to extrastriate cortex are cortical areas that are highly specialized for face processing [Haxby et al., 1994]. In particular, bilateral lingual/fusiform gyri and the right parahippocampal gyrus are almost always involved in facial processing [Kapur et al., 1995]. Processing of faces in this area takes place within 165 ms [Halgren et al., 2000] and the amygdala is required to link visual representations of facial expressions with affective representations such as fear [Adolphs et al., 1995]. Some groups have suggested that the amygdala is more sensitive to fear relative to other emotional expressions [Morris et al., 1996], and is involved even in the absence of awareness [Whalen et al., 1998], which may be mediated via subcortical pathway to the right amygdala, via midbrain and thalamus [Morris et al., 1999]. Moreover, an extended circuitry comprising the amygdala, pulvinar, anterior insula, and anterior cingulate activates during the processing of fearful faces [Morris et al., 1998b], which also appears to be engaged whenever an explicit emotion face judgment is required [Gorno-Tempini et al., 2001]. Some investigators have argued that left and right amygdala and extended limbic areas are differentially involved in negative versus positive emotion processing, respectively. For example, left amygdala activity was associated with stronger activation during negative valenced face presentation. In comparison, right amygdaloid activity was stronger when positive facial expressions were evaluated [Iidaka et al., 2001]. Others have found emotional expressions of happiness, fear, and sadness but not anger are recognized more efficiently in the right versus the left hemisphere [Indersmitten and Gur, 2003]. This notion is consistent with findings of exaggerated left but not right amygdala response to masked faces in depressed subjects [Sheline et al., 2001]. Based on studies with brain lesion individuals, it appears that the right inferior parietal cortex and the right mesial anterior infralcalcarine cortex is important for the recognition of an emotion in pictures of faces [Adolphs et al., 1996]. Moreover, holding emotional faces in mind is associated with differential activity in left ventral prefrontal cortex, the left anterior cingulate cortex, and the right fusiform gyrus [Dolan et al., 1996]. Recently, some investigators have argued that the amygdala is able to process complex social emotions such as guilt, admiration, or flirtatiousness [Adolphs et al., 2002]. Therefore, even seemingly “simple” paradigms such as
emotional face processing are composed of complex emotional and cognitive component processes. Thus, it is important to better delineate which components may be dysfunctional in individuals with anxiety disorders.

The neural substrates underlying executive functioning, e.g., the dorsolateral prefrontal cortex and the anterior cingulate, modulate the activation of amygdala and the extended limbic system [Nomura et al., 2004]. Specifically, inversely correlated activation has been observed in these areas in relation to the amygdala and are thought to contribute to conscious evaluation and appraisal [Hariri et al., 2003, 2002]. These findings are consistent with recent report of an altered relationship between amygdala activation and MPFC [Pezawas et al., 2005] and can be disaggregated using multivariate statistical approaches [Keightley et al., 2003]. Others have also found a strong attention-related modulation in the orbitofrontal cortex during emotional face processing [Monk et al., 2003], which may give rise to representations of somatic markers, i.e., “gut feelings,” associated with facial emotions [Winston et al., 2003].

Several groups have begun to relate emotional face processing to anxiety. For example, low-anxiety subjects but not high-anxiety subjects were found to show reduced amygdala response to unattended versus attended fearful faces. Moreover, latter group show an increased amygdala response to fearful versus neutral faces regardless of attentional focus [Bishop et al., 2004]. Others have proposed that high trait anxious individuals show enhanced unconscious processing of emotional faces, which has been attributed to activation in the basolateral amygdala [Etkin et al., 2005]. Some have suggested that the insula plays a unique role in the processing of threat signals in subjects with anxiety disorders [Straube et al., 2004]. In summary, the neural circuitry underlying emotional face processing has been well delineated and consists of limbic and paralimbic “bottom up” processing circuits and cortical “top-down” processing circuits.

Taken together, several key structures are hypothesized to modulate the basic anxiety circuitry. First, the amygdala is critical for assigning valence or salience to environment and internal stimuli. Second, the insular cortex is important for the processing of interoception and predictive interoception, i.e., how the body feels and how it may feel given a predictive internal or environmental stimulus. Third, the MPFC including the anterior cingulate is important for cognitive and affective conflict as well as self-relevant processing and evaluates the degree to which one needs to deploy executive control in response to environmental demands.

ANXIETY PHENOTYPES

Anxiety is a normal emotion if the arousing and motivating interoception is due to significant internal or external stimuli and can be used to deploy new cognitive or behavioral strategies. However, altered levels of anxiety may be due to several different dysfunctional neural circuit processes. First, increased amygdala may drive the insular too much, i.e., normal interoceptive stimuli acquire aversive valence or salience. Second, insular cortex may “overpredict” aversive outcomes and therefore predictive stimuli are associated with hyperamygdala response. Third, general heightened arousal level may result in aversive “tagging” of predictive stimuli as aversive, which leads to increased anxiety. The neural circuit model, which we have proposed recently, is consistent with recent psychological conceptualizations of anxiety disorders. Together with temperamental vulnerabilities, which can be viewed as diatheses that make certain individuals more susceptible to adverse and stressful experiences, altered learning processes can result in the development of anxiety disorders [Mineka and Zinbarg, 2006]. Of the anxiety disorders, two are of particular interest because the processes that initiate or maintain them may differ, whereas the neural substrates might be quite overlapping and support the generalizability of our proposed model.

First, the development of PD has been described by some [de Beurs et al., 2002] as a process they termed “fear of fear” developing from interoceptive conditioning. In particular, the match–mismatch model of panic states that PD patients tend to overestimate the probability of panic prior to engaging in a fear-provoking situation [de Beurs et al., 2002]. This is part of the general mismatch prediction model, which states that people overestimate how frightened they will be when faced by a fear-provoking situation [Rachman, 1994]. Second, several psychological theories have proposed that uncontrollable and unpredictable aversive events may play an important role in the development of generalized anxiety disorder [GAD; Barlow et al., 1986; Mineka and Hendersen, 1985]. Specifically, people with GAD have far less tolerance for uncertainty than do non-anxious controls [Dugas et al., 1998] and they are especially disturbed by not being able to predict the future [Roemer et al., 1997]. Therefore, whereas PD may be a form of “bottom up” failure, i.e., may be due to altered modulation of interoceptive signals, GAD may be due to an altered “top down” modulation. In both cases, however, we predict that these individuals will show altered connectivity in the basic anxiety circuitry.

This altered “bottom up” or “top down” modulation is not unlike processes that have been described in the pain physiology literature as the basis for allodynia, i.e., the perception of innocuous stimuli as being painful and aversive. Interestingly, the same neural circuitry that we propose to comprise the basic anxiety circuit is also involved in allodynia. For example, in a recent study, the intensity of allodynic pain was directly related to the degree of activation in the caudal anterior insular cortex [Schweinhardt et al., 2006], which is an area that has been reported to code for the intensity of perceived pain [Craig et al., 2000] as opposed to...
ongoing pain intensity, which has been found to correlate with rostral anterior insula [Petrovic et al., 2002].

Thus, one may be able to distinguish an altered "top down" modulation of the basic anxiety circuitry, which will manifest in some individuals, such that the executive, cognitive control system attempts to downregulate this system by cognitive activity, i.e. worrying. This results in the GAD phenotype. In contrast, altered "bottom up" modulation will be present in individuals who do not use extensive cognitive control (worry) and will therefore experience episodes of unconstrained fear and associated physical symptoms. This is the PD phenotype; many of these individuals will avoid environments that are associated with insula–amygdala hyperactivity. This is the agoraphobia phenotype.

Thus, although many studies have been carried out with specific anxiety disorder groups, it is not clear whether the imaging phenotypes proposed here will follow the somewhat arbitrary conventional distinction of Diagnostic Statistics Manual—IV-TR (DSM IV-TR) categories of anxiety disorders. Nevertheless, it is useful to briefly summarize the main findings in selected anxiety disorders. Individuals with generalized social phobia show significant increased activation during contemptuous face processing in left allocortex, which includes amygdala, uncus, and parahippocampal gyrus [Stein et al., 2002]. Similarly, relative to happy faces, activation of the amygdala in response to harsh (angry, disgusted, fearful) faces was greater in these patients than in controls, and the extent of amygdala activation was positively correlated with severity of social anxiety symptoms [Phan et al., 2006]. Generalized social phobia patients, however, show reduced neural activation related to implicit learning compared with healthy comparison subjects in the left caudate head, left inferior parietal lobe, and bilateral insula [Sareen et al., 2007]. Posttraumatic stress disorder is characterized by an exaggerated amygdala response, which may subserve exaggerated acquisition of fear associations and expression of fear responses, and deficient frontal cortical function, which may mediate deficits in extinction and the capacity to suppress attention/response to trauma-related stimuli, as well as deficient hippocampal function, which may be responsible for deficits in appreciation of safe contexts and explicit learning/memory [Rauch et al., 2006]. In pain-related experiments, patients with Post-Traumatic Stress Disorder (PTSD) rated temperatures as less painful compared with controls but show increased activation in the left hippocampus and decreased activation in the bilateral ventrolateral prefrontal cortex and the right amygdala [Geuze et al., 2007]. Phobic individuals show early amygdala-related picture-processing abnormalities. In particular, amygdalar BOLD responses associated with timing but not magnitude of activation predicted affective responses to phobogenic stimuli [Larson et al., 2006]. Patients with PD display less amygdala activation but greater cingulate cortex activation than controls in response to fearful faces [Pillay et al., 2006]. In obsessive–compulsive disorder (OCD), color naming OCD-related, but not PD-related, words was found to correlate with increased activation of frontal-striatal and temporal regions. In contrast, an increased frontal-striatal involvement was found during color naming both OCD-related and panic-related words in PD patients [van den Heuvel et al., 2005]. Baseline perfusion of the orbitofrontal cortex predicted panic attacks such that lower perfusion was associated with heightened anxiety in response to a pharmacological challenge [Kent et al., 2005]. Others have found that OCD subjects exhibited a weaker response than control subjects bilaterally across all face conditions versus fixation in the amygdala [Cannistraro et al., 2004]. Therefore, although there are some distinctions in processing-related activation differences across diagnostic groups, it is not clear how reliable and specific these differences are because of the lack of large studies with multi-diagnostic groups.

Apart from different neural substrate-based-processing dysfunction derived anxiety phenotypes, one can begin to examine the effect of anti-anxiety treatments on healthy individuals or patients with anxiety disorders. This approach can be useful to determine whether neuroimaging tools could become (1) a bioassay for developing novel treatments for anxiety disorder, or (2) a way of monitoring treatment success during longitudinal studies, or (3) to measure the risk for developing another symptomatic episode of a particular anxiety disorder.

A recent neuroimaging study showed that right amygdala response to aversive faces was attenuated by citalopram [Del Ben et al., 2005]. Others have reported that after treatment with citalopram, worry sentences, compared with neutral statements, elicit reduced BOLD responses in prefrontal regions, the striatum, insula, and paralimbic regions [Hoehn-Saric et al., 2004]. Finally, citalopram also reduced responses within the hippocampus and MPFC specifically during the fear-relevant stimuli [Harmen et al., 2006]. Thus, serotonin-specific reuptake inhibitors, which are standard treatment for many anxiety disorders, alter process-related all three key neural substrates that were summarized above. Some investigators have argued that individuals whose pretreatment amygdala activity is the strongest may be particularly likely to respond well to such widely used treatments as selective serotonin reuptake inhibitor (SSRI) medications and CBT [McClure et al., 2007]. Novel treatment approaches may also be good candidates for imaging studies to better understand how they affect anxiety disorders. For example, oxytocin relative to placebo potently reduced activation of the amygdala and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear [Kirsch et al., 2006].
Anxiety-prone subjects had significantly greater bilateral amygdala and insula activation to emotional faces than did the anxiety-normative comparison subjects [Stein et al., 2007]. Similarly, basolateral amygdala to unconscious stimuli and subjects’ reaction times were predicted by individual differences in trait anxiety [Etkin et al., 2004]. Finally, behaviorally inhibited individuals relative to healthy adolescents show an exaggerated amygdala response during subjective fear ratings and deactivation during passive viewing, across all emotion faces [Perez-Edgar et al., 2007]. In comparison, neither high- nor low-anxious volunteers showed an increased amygdala response to threat distractors. However, under low perceptual load, elevated state anxiety was associated with a heightened response to threat distractors in the amygdala and superior temporal sulcus, whereas individuals high in trait anxiety showed a reduced prefrontal response to these stimuli, consistent with weakened recruitment of control mechanisms used to prevent the further processing of salient distractors [Bishop et al., 2006]. Taken together, there are several studies that show individuals who are at risk for an anxiety disorder show brain-processing differences that are quantitatively similar to those observed in anxiety disorder patients. Other groups have investigated the role of specific candidate genes to alter anxiety-related processing and therefore potentially serve as vulnerability genes. For example, the 5-HTTLPR (serotonin transporter) gene polymorphism has a powerful effect on amygdala reactivity to environmental threat. Although, the 5-HTTLPR gene is not specifically related to an anxiety or mood disorder, it may represent a classic susceptibility factor [Hariri et al., 2005]. Others have pointed to the dopamine neurotransmission associated with the met allele of the COMT polymorphism, which is associated with heightened reactivity and connectivity in corticolimbic circuits [Drabant et al., 2006]. Functional analysis of those regions during perceptual processing of fearful stimuli demonstrated tight coupling as a feedback circuit implicated in the extinction of negative affect. Finally, short-allele carriers of the 5-HTTLPR gene show relative uncoupling of the MPFC amygdala circuit [Pezawas et al., 2005].

One of the major challenges for neuroimaging to play a critical clinical role is to determine its sensitivity and specificity. Thus far, most imaging studies have revealed intriguing systems neuroscience results on a group level, however, these findings are insufficient to help move imaging forward clinically. On the other hand, most imaging studies have demonstrated surprisingly large effect sizes, which would support the idea that differences across individuals and across time within individuals may be large enough to be meaningfully measured on a subject by subject basis. To be useful as an illness severity marker, neuroimaging measures need to closely track disease state both when it is symptomatic as well as when the disorder is asymptomatic. Thus, it is not sufficient to show that ill individuals differ from healthy subjects but also that recovered or asymptomatic anxiety disorder individuals have altered processing levels implemented in specific brain structures when compared with those individuals without an anxiety disorder. The latter will enable one

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**Figure 1.** The process of the role of brain imaging in anxiety disorders is shown. Specifically, we propose that functional neuroimaging is not about a particular brain area but about the interaction between the process and the brain system. Therefore, it is important to clarify the role of brain structure involvement in relation to the process that is being tested.
to make clinical predictions about individuals who are at high risk for experiencing exacerbation of their anxiety symptoms sometimes in the future. As pointed out above, neuroimaging is not useful in isolation but needs to be considered within the context of the process that the brain substrates are carrying out. Here, again, results from studies examining both amygdala and insular cortex function offer some insight into the direction of the clinical use of neuroimaging. Clearly, functional neuroimaging will play an important role in anxiety disorder research, however, in order for this modality to be useful for defining diagnostic categories or monitoring treatment success, one will need to push the limits of this technology to clearly show its ability on a single-subject basis. (Fig. 1).

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