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The Role of Neuroimaging for the Diagnosis and Treatment of Anxiety Disorders

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Abstract

Neuroimaging comprises a set of tools, which include different types of magnetic resonance imaging such as fMRI, MRS, ASL, and radiotracer imaging such as PET and SPECT. The focus of this review is to address the question whether functional magnetic resonance imaging (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.

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 [1]. Deoxyhemoglobin has paramagnetic effects in the blood upon the nuclear magnetic resonance transverse relaxation times of nearby water protons in the tissue [2]. 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) functional magnetic resonance imaging (fMRI) [3]. Recent BOLD fMRI experiments in the awake

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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 [4]. Moreover, increases in baseline blood flow is thought to be proportional to total deoxyhemoglobin within a voxel [5]. For example, increased baseline cerebral blood flow by breathing CO2 reduces the BOLD response to the same task substantially [6]. Therefore, the BOLD signal reflects the effect of neural activity on dynamic changes in cerebral blood flow (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 bio-assay. 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 [7,8]. However, this structure is also important for other emotional information processing and behavior [9]. Functional neuroimaging studies have shown amygdala activation in fear conditioning [10], reward related processing [11], encoding of emotionally salient information [12], risk-taking [13], processing positively valenced stimuli [14], and appetitive or aversive olfactory learning [15]. Individuals with social anxiety disorder [16] or posttraumatic stress disorder [17] show amygdala hyperresponsivity to fearful or angry faces. In addition to the amygdala changes, panic disorder patients have decreased benzodiazepine receptor binding in left hippocampal and precuneus [18] and in right orbitofrontal cortex and right insula [19].

In addition to the amygdala, a network of structures which includes the insula, anterior cingulate gyrus and medial prefrontal cortex are important for the identification of the emotional significance of a stimulus, to generate an affective response, and to regulate the affective state [20]. The insula (for review see [21,22]) 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 [23]. 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 [24]. The columnar organization of the insular cortex shows an highly organized anterior inferior to posterior superior gradient (for example see [25]). Specifically, whereas posterior insular is characterized by a granular cortical architecture, the anterior inferior insula has an agranular columnar organization, i.e. lacks layer 4 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 [26]. Finally, the discovery of spindle cells within the anterior insular –orbitofrontal transition region [27] 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 [28,29]. The insula has afferent and efferent connections to medial and orbitofrontal cortex, anterior cingulate and several nuclei of the amygdala [21]. Although insula activation has been frequently associated with disgust [30], there is increasing evidence of a broader role for this brain structure in emotion processing [31]. Insula activation is thought to be involved in differential positive versus negative emotion processing [32], in particular fearful face processing [33], pain perception [34,35], and when individuals were asked to make judgments about emotions [36].

The medial prefrontal cortex, 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-medial prefrontal cortex and lateral prefrontal regions, premotor cortex, parietal and occipital cortex, caudate and cerebellum [37]. Other investigators have shown that activity in medial prefrontal cortex predicted both subsequent memory performance and judgments of self-relevance [38,39]. More specifically, individuals while making judgments about trait adjectives under three experimental conditions (self-relevance, other-relevance, or case judgment) show that the medial prefrontal cortex was selectively engaged during self-referential processing [38], 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 [40].

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 to a letter task [41]. These evaluative judgment 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 [42]. 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” [43]. 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 medial prefrontal cortex (MPFC), and additionally recruited dorsal medial frontal regions and insula as the extent of self-relatedness increased [44]. Taken together, medial prefrontal cortex regions may contribute to the neural instantiation of aspects of the multifaceted “self” [45]. Thus, amygdala, insula, and medial prefrontal cortex 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 [46]. In particular, bilateral lingual/fusiform gyri and the right parahippocampal gyrus are almost always involved in facial processing [47]. Processing of faces in this area takes place within 165 ms [48] and the amygdala is required to link visual representations of facial expressions with affective representations such as fear [49]. Some groups have suggested that the amygdala is more sensitive to fear relative to other emotional expressions [50], and is involved even in the absence of awareness [51], which may be mediated via subcortical pathway to the right amygdala, via midbrain and thalamus [52]. Moreover, an extended circuitry comprising the amygdala, pulvinar, anterior insula and anterior cingulate activates during the processing of fearful faces [53], which also appears to be engaged whenever an explicit emotion face judgment is required [36]. 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 [54]. Others have found emotional expressions of happiness, fear, and sadness but not anger are recognized more efficiently in the right versus the left hemiface [55]. This notion is consistent with findings of exaggerated left but not right amygdala response to masked faces in depressed subjects [56]. Based on studies with brain lesion individuals, it appears that the right inferior parietal cortex and the right mesial anterior infracalcarine cortex is important for the recognition of an emotion in pictures of faces [57]. 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 [58]. Recently, some investigators have argued that the amygdala is able to process complex social emotions such as guilt, admiration or flirtatiousness [59]. Therefore, even seemingly “simple” paradigms such as emotional face processing are comprised 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 [60]. 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 [61,62]. These findings are consistent with recent report of an altered relationship between amygdala activation and medial prefrontal cortex [63] and can be disaggregated using multivariate statistical approaches [64]. Others have also found a strong attention related modulation in the orbitofrontal cortex during emotional face processing [65], which may give rise to representations of somatic markers, i.e. “gut feelings”, associated with facial emotions [66].

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 [67]. 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 [68]. Some have suggested that the insula plays a unique role in the processing of threat signals in subjects with anxiety disorders [69]. 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 medial prefrontal cortex 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 hyper-amygdala 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 [70]. 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 panic disorder has been described by some [71] as a process they termed “fear of fear” developing from interoceptive conditioning. In particular, the match-mismatch model of panic states that panic disorder patients tend to overestimate the probability of panic prior to engaging in a fear-provoking situation [71]. 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 [72]. Second, several psychological theories have proposed that uncontrollable and unpredictable aversive events may play an important role in the development of GAD [73,74]. Specifically, people with GAD have far less tolerance for uncertainty than do nonanxious controls [75] and they are especially disturbed by not being able to predict the future [76]. Therefore, whereas panic disorder may be a form of “bottom up” failure, i.e. may be due to altered modulation of interoceptive signals, generalized anxiety disorder 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 [77], which is an area that has been reported to code for the intensity of perceived pain [78] as opposed to ongoing pain intensity, which has been found to correlate with rostral anterior insula [79].

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 down-regulate 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 Panic Disorder (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 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 [16]. 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 [80]. 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 [81]. Post-traumatic 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 [82]. In pain-related experiments, patients with 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 [83]. 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 [84].

Patients with Panic disorder display less amygdala activation but greater cingulate cortex activation than controls in response to fearful faces [85]. 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 Panic Disorder patients [86]. Baseline perfusion of the orbitofrontal cortex predicted panic attacks such that lower perfusion was associated with heightened anxiety in response to a pharmacological challenge [87]. Others have found that OCD subjects exhibited a weaker response than control subjects bilaterally across all face conditions versus fixation in the amygdala [88]. 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 [89]. Others have reported that after treatment with citalopram, worry sentences, compared to neutral statements, elicit reduced BOLD responses in prefrontal regions, the striatum, insula and paralimbic regions [90]. Finally, citalopram also reduced responses within the hippocampus and medial prefrontal cortex specifically during the fear-relevant stimuli [91]. 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 [92]. 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 [93].

Anxiety-prone subjects had significantly greater bilateral amygdala and insula activation to emotional faces than did the anxiety-normative comparison subjects [94]. Similarly, basolateral amygdala to unconscious stimuli, and subjects' reaction times, were predicted by individual differences in trait anxiety [68]. 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 [95]. 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 [96]. 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 [97]. 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 [98]. 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 medial prefrontal cortex amygdala circuit [63].

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 to those individuals without an anxiety disorder. The latter will enable one 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.

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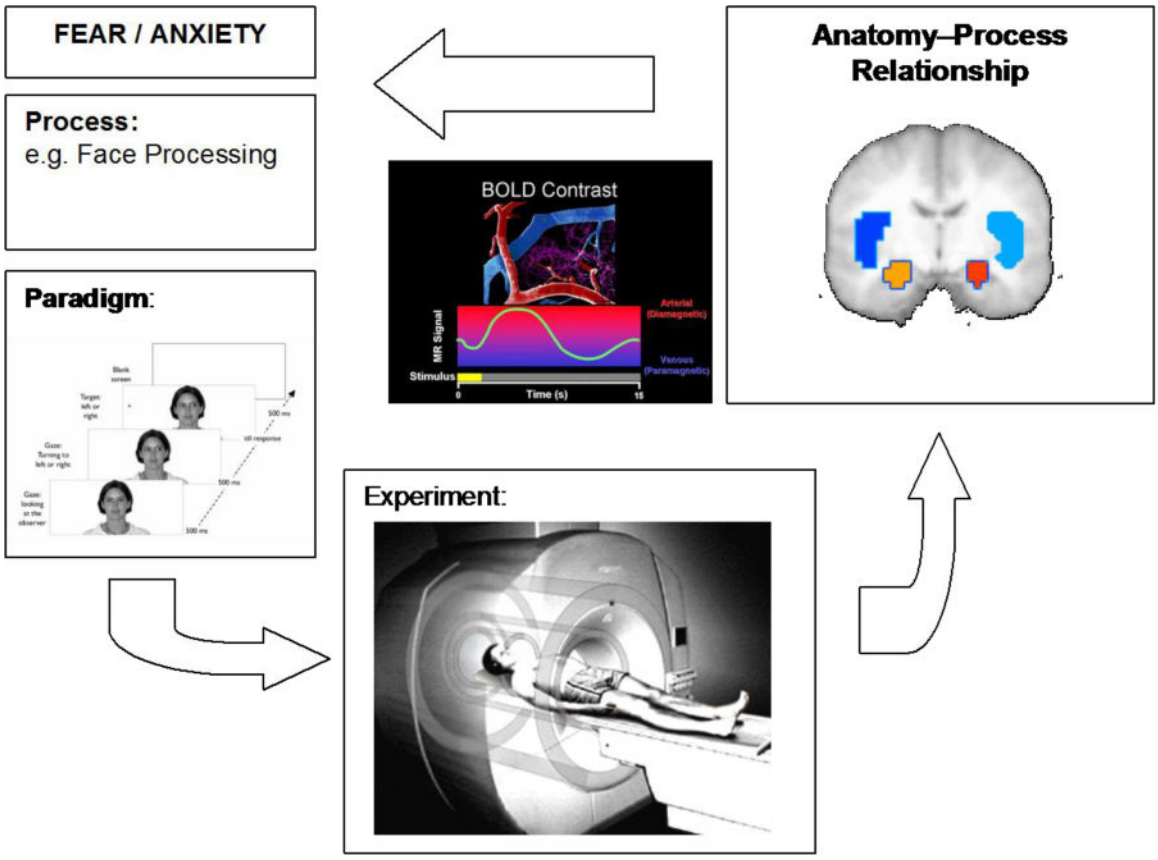

Figure 1.

This figure shows the process of the role of brain imaging in anxiety disorders. 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.