

# Pathological anxiety and function/dysfunction in the brain's fear/defense circuitry

Peter J. Lang\*, Lisa M. McTeague and Margaret M. Bradley  
*Center for the Study of Emotion & Attention, University of Florida, FL, USA*

**Abstract.** Research from the University of Florida Center for the Study of Emotion and Attention aims to develop neurobiological measures that objectively discriminate among symptom patterns in patients with anxiety disorders. From this perspective, anxiety and mood pathologies are considered to be brain disorders, resulting from dysfunction and maladaptive plasticity in the neural circuits that determine fearful/defensive and appetitive/reward behavior (Insel et al., 2010). We review recent studies indicating that an enhanced probe startle reflex during the processing of fear memory cues (mediated by cortico-limbic circuitry and thus indicative of plastic brain changes), varies systematically in strength over a spectrum-wide dimension of anxiety pathology—across and within diagnoses—extending from strong focal fear reactions to a consistently blunted reaction in patients with more generalized anxiety and comorbid mood disorders. Preliminary studies with functional magnetic resonance imaging (fMRI) encourage the hypothesis that fear/defense circuit dysfunction covaries with this same dimension of psychopathology. Plans are described for an extended study of the brain's motivation circuitry in anxiety spectrum patients, with the aim of defining the specifics of circuit dysfunction in severe disorders. A sub-project explores the use of real-time fMRI feedback in circuit analysis and as a modality to up-regulate circuit function in the context of blunted affect.

**Keywords:** Imagery, anxiety, specific phobia, social phobia, panic, GAD, comorbidity, depression, PTSD, trauma, chronicity, emotional reactivity, diagnostic subtypes, psychophysiology, startle, fMRI, real-time fMRI

Pathological anxiety is poorly understood from the perspectives of both its basic mechanism and diathesis—most obviously in terms of objective neurobiological measures. The current accepted method for classifying principal anxiety disorders, the clinical interview, is overwhelmed by comorbidities and lacks specificity in defining targets for treatment. Our best therapies are aimed at reducing fear arousal, a presumed general factor in these disorders, but the overall

therapy success rate is little over fifty percent of treated patients.

Responding to these concerns as they pertain to all functional pathologies, the U.S. National Institute of Mental Health (NIMH) has recently proposed a new strategy for implementation by the research community. Called the Research Domain Criteria (RDoC) initiative, it is described in the NIMH's current Strategic Plan (Strategy 1.4): To “develop for research purposes, new ways of classifying disorders based on dimensions of observable behavior and neurobiological measures” (See also, Insel & Cuthbert, 2009; Cuthbert & Insel, 2010; Insel et al., 2010; Insel & Wang, 2010). The research presented here and the

\*Corresponding author: Peter J. Lang, PhD, Center for the Study of Emotion & Attention, University of Florida, PO Box 112766, Gainesville, FL 32611, USA. Tel.: +1 352 392 2439; Fax: +1 352 392 6047; E-mail: plang@phhp.ufl.edu.

intended future development are consistent with this general plan.

### 1. From fear to “anxious misery”: Factor analyses

Over the last decade researchers have become increasingly aware of the ubiquity of anxiety disorder co-morbidity (i.e., dysthymia/depression and other clinically significant anxiety diagnoses), the consequent low incidence of “pure” cases, and resulting problems in understanding the determinants of anxiety pathology. Factor analyses suggest that the different anxiety diagnoses may not be unitary phenotypes as assumed by current assessment practice (DSM-IV-TR, APA, 2000), and furthermore, that there may be latent dimensions of pathology that overlap with mood disorders and might better capture the anxiety diathesis. For example, in an analytic study of the National Comorbidity Survey, Krueger (1999) reported dramatically high disorder covariations among “internalizing (anxiety/depression) disorders within two discriminable factor subsets, one characterized by intense “fear” (phobic disorders) and a second factor that included generalized anxiety disorder (GAD), dysthymia, and major depression, labeled “anxious misery”. He also noted “the positive association between comorbidity and severity of psychopathological dysfunction, and proposed that the factor analytic model that grouped disorders with shared variance might better guide the search for a “genetic etiology”.

Subsequent genetic epidemiological research has since significantly advanced this approach (e.g., Hettema et al., 2005; Kendler et al., 2003; Tambs et al., 2009). In a study of more than 5000 twin pairs, Hettema et al. (2005) determined that “the genetic influences on anxiety were best explained by 2 additive genetic factors common across disorders. The first ( $A_1$ ) loaded most strongly in generalized anxiety disorder, panic disorder, and agoraphobia, whereas the second ( $A_2$ ) loaded primarily in the two specific phobias.” (Animal and Situational type)

Research has also addressed the hypothesis that comorbidity among the internalizing disorders may reflect underlying personality traits that extend from normal levels in the general population to pathological levels in the anxious and mood disorders (e.g., Bienvendu et al., 2001). Hettema et al. (2006) assessed differences in the genetic variance related

to the Eysenck Neuroticism Scale and an estimate of Questionnaire-independent (non-specific) genetic variance in his twin sample. In this research the internalizing disorders showed significant loadings on both genetic factors; for fear disorders, however, only one genetic component, the neuroticism related factor, showed a significant loading for animal and situational phobias—again suggesting a separate diathesis for fear and anxious misery.

Together, these findings suggest that there is a spectrum dimension of pathology extending from diagnoses primarily associated with specific fears to more severe, generalized, highly comorbid diagnoses that can be characterized as chronic “anxious misery”.

### 2. The fear/defense circuit and startle potentiation

Neuroscience researchers (Falls et al., 1992; Gloor, 1960; Gray, 1989; Kapp & Pascoe, 1986; Kapp et al., 1984; LeDoux, 1987; Sarter & Markowitsch, 1985) have described a fear/defense circuit primarily seated in the limbic brain. Activation of this circuit begins when the lateral and basolateral nuclei of the amygdala receive threat-relevant information from sensory/memory cues. These nuclei project to the amygdala’s central nucleus and the bed nucleus of the stria terminalis, which in turn project to a variety of hypothalamic sites, the central gray, facial motor nucleus, and brainstem target areas, initiating a range of defensive reflexes that evolved to counter imminent threats to survival (cf. Lang and Davis, 2006). Significant among the reactions mediated by this circuit is potentiation of the startle reflex. Led by Michael Davis (e.g., Davis, 2000; Davis and Lang, 2003), neuroscience studies consistently find that prior fear-conditioning in rodents significantly enhances the reflex, providing a metric for the assessment of defense system activation, and indirectly, the fear state.

In humans, startle reactions in the conditioned shock-fear paradigm are comparable to those found with animals. Importantly, research first generated in our laboratory found that startle reflexes are also potentiated when participants process any unpleasant/fear cues, even images from the media (Vrana et al., 1988; Lang et al., 1990). Thus, healthy individuals show augmented probe reflex responses when they look at pictures of unpleasant objects or events (Bradley, Codispoti, Cuthbert et al., 2001; Bradley, Codispoti,

Sabatinelli, et al., 2001) and when they recall fearful memories or imagine fearful scenarios (Vrana & Lang, 1990). It is also clear that participants who report high fear to typical phobic objects (e.g., snakes, spiders, blood) show exaggerated fear potentiation when looking at their pictorial representations (Hamm, et al., 1997; Sabatinelli et al., 2001) or when reliving fear experiences in imagination (Cuthbert et al., 2003; Vrana & Lang, 1990).

### 3. Startle potentiation and the anxiety disorders

The assumption of brain circuit hyperactivity as a determinant of the anxious state suggests that disorder relevant fear cues, regardless of the specific anxiety diagnosis, predicts uniformly greater probe startle potentiation than is found in healthy participants. Individual studies of patient groups with a common principal diagnosis have appeared to support this assumption (e.g., see Davis et al., 2010 for a recent survey). Importantly, however, issues of negative affectivity, disorder complexity, chronicity, severity, and comorbidity have generally not been addressed.

In our own research assessing a broad spectrum of anxiety patients, magnitude of startle reactivity has been shown to vary dramatically across diagnoses. Startle reflexes are measured during text-driven fear memory imagery, a methodology commonly used in the assessment and treatment of anxiety disorders (Orr et al., 1998; Pitman et al., 1987; Foa, 2006). Participants imagine being actively involved in clinically-relevant narratives—both standard as well as idiographic feared scenarios. Presumptive evidence was first obtained in a study ( $N=130$ ; Cuthbert et al., 2003) of 4 disorders (specific phobia; social phobia; panic disorder with agoraphobia, PDA; & posttraumatic stress disorder, PTSD), showing hyper-reactivity during aversive imagery in focal fear, but a significantly decreasing reflex response for disorders characterized as more severe, chronic and comorbid.

In a subsequent more extensive study, over four hundred treatment seeking anxiety patients and 75 healthy control participants were assessed (Lang et al., 2005, 2007; Lang & McTeague, 2009; McTeague & Lang, 2012). Startle probe potentiation during fearful memory imagery was the primary measure. As illustrated in the top panel of Fig. 1 the startle reflex is reliably potentiated in specific phobia patients

when imagining their phobic object/context (Lang & McTeague, 2009). However, large differences in fear potentiation were observed over the spectrum of anxiety disorders, with panic disorder with agoraphobia (PDA) and generalized anxiety disorder (GAD) groups failing to show evidence of exaggerated startle when imagining personally relevant fear scenes. Moreover, the average BDI scores for these patients (bottom panel of Fig. 1) showed a linear trend across the anxiety disorder spectrum, but one that is opposite in direction to the startle potentiation gradient, with the highest BDI scores associated with the least fear potentiation. Similar relationships are apparent for other clinical measures, including a mounting incidence of co-morbid major depression and the number of co-morbid anxiety disorders; increasing scores on questionnaire measures of non-specific anxiety, interoceptive sensitivity, and functional interference. In effect, the magnitude of startle potentiation appears to vary reciprocally with measures of anxiety generalization, severity, and trait negative affectivity.

#### 3.1. Within-diagnosis variability

Subsequent research has found, furthermore, that differences apparent across the spectrum are also seen within DSM diagnostic categories—again related to the variables of negative affect, chronicity, severity, and mood that characterize diagnostic differences in reflex reactivity. For instance, in a study of posttraumatic stress disorder (Lang & McTeague, 2011; McTeague et al., 2010), PTSD patients were divided into those who had experienced a single traumatic event and those with a history of multiple traumas. Whereas the single trauma group showed dramatic startle potentiation during personal fear imagery (Fig. 2), the multiple trauma group showed much reduced fear potentiation and higher ratings of *negative affectivity* (Fig. 3) as well as increased incidence of co-morbid depression and other anxiety diagnoses, longer chronicity (in years), and higher interview ratings of disorder severity.

A similar pattern of reactivity is found for panic disorder (Fig. 4): Patients without agoraphobia show significant fear potentiation during fear-relevant imagery, whereas panic disorder patients with agoraphobia show blunted reflex reactivity that increases with agoraphobia severity (McTeague et al., 2011). Again, obtunded probe startle reflexes were accompanied by an increase in broad self-reported *negative affectivity* (Fig. 5).

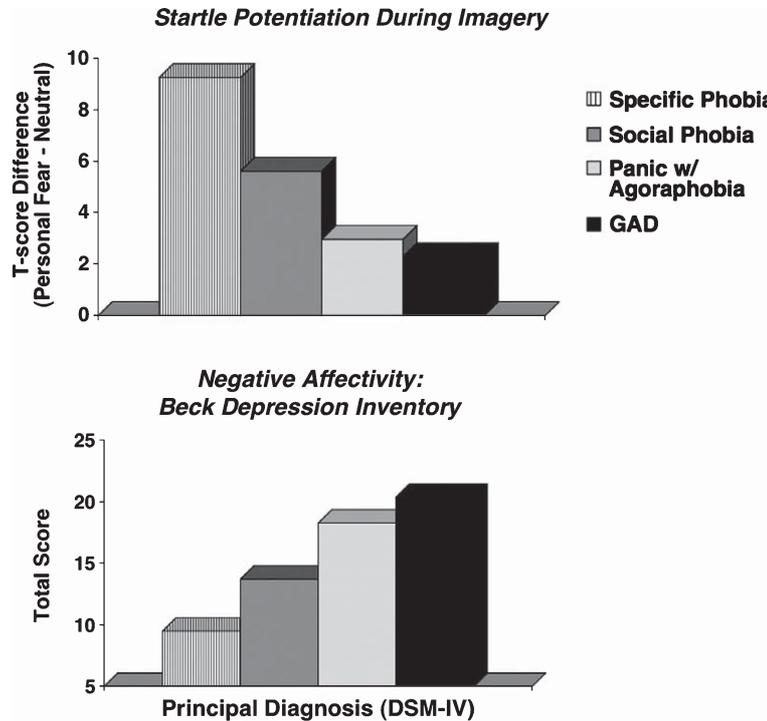


Fig. 1. Top Panel. Mean fear potentiation of startle reflexes (startle response magnitude during personal threat minus neutral imagery) for patients by principal disorder (GAD = generalized anxiety disorder) as determined with the Anxiety Disorders Interview Schedule for DSM-IV (Brown et al., 1994), arranged in order of decreasing response magnitude and coincidentally—decreasing fear specificity. Bottom panel. Mean total score reported on the Beck Depression Inventory (Beck et al., 1996) by principal disorder showing an inverse relationship between fear potentiation and self-reported negative affectivity.

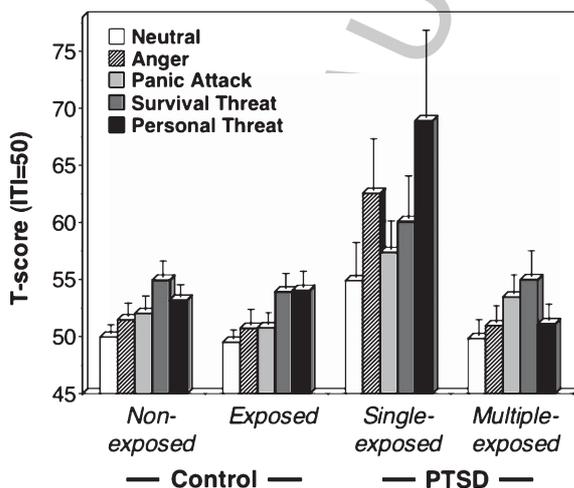


Fig. 2. Mean startle reflex responses standardized to the distribution of responses during intertrial intervals during neutral, anger, panic, survival threat, and personal threat imagery for non-exposed and trauma-exposed control groups and single- and multiple-trauma PTSD groups. Error bars refer to standard error of the mean. Adapted from McTeague and colleagues (2010).

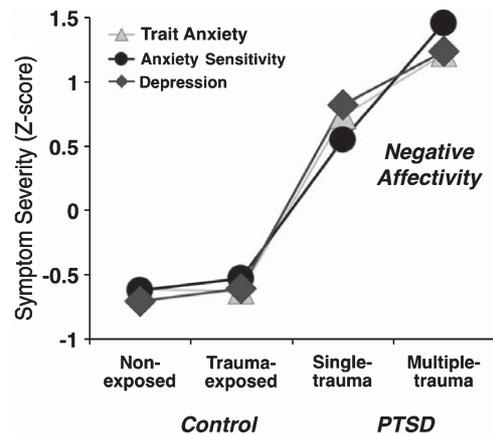


Fig. 3. Group means (standardized across participants) on the trait form of the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983), Anxiety Sensitivity Index (Reiss et al., 1986), and Beck Depression Inventory (Beck et al., 1996) showing progressive increases in negative affectivity from non-exposed and trauma-exposed control groups to single- and finally multiple-trauma PTSD. Adapted from McTeague and colleagues (2010).

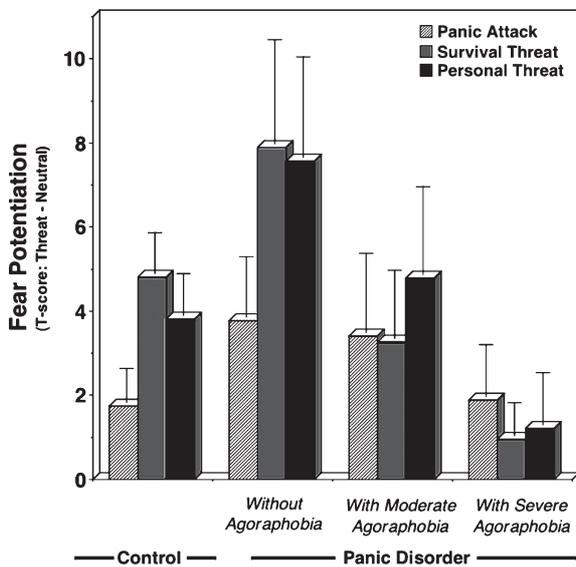


Fig. 4. Mean fear potentiation of startle reflexes (startle response magnitude during threat minus neutral imagery) during standard panic attack and survival threat as well as personal threat imagery for control participants and patients with principal panic disorder without agoraphobia, with moderate agoraphobia, and with severe agoraphobia.

Results were comparable for patients diagnosed with principal social anxiety: Circumscribed social phobia patients show strong startle potentiation during imagery of their performance fear (Fig. 6), but only a modest increase for social fear narratives unrelated to their performance fear. For the non-depressed generalized social phobia patients, all social threat scenes show markedly potentiated startle reflexes. A significant reduction in potentiation is, however, clearly apparent in generalized social anxiety patients with comorbid major depression. The differences among social anxiety patients were not limited to depression, however, but again included co-varying higher symptom reports of fearfulness and anxiety, consistent with a generally enhanced *negative affectivity* (Fig. 7; McTeague et al., 2009).

#### 4. The diagnostic spectrum

Figure 8 shows startle potentiation during patients personal “greatest fear” (relative to neutral imagery) as in Fig. 1, expanded here to illustrate reactivity across the entire anxiety spectrum, including all principal diagnoses and their subtypes ( $N = 478$ ). Although startle

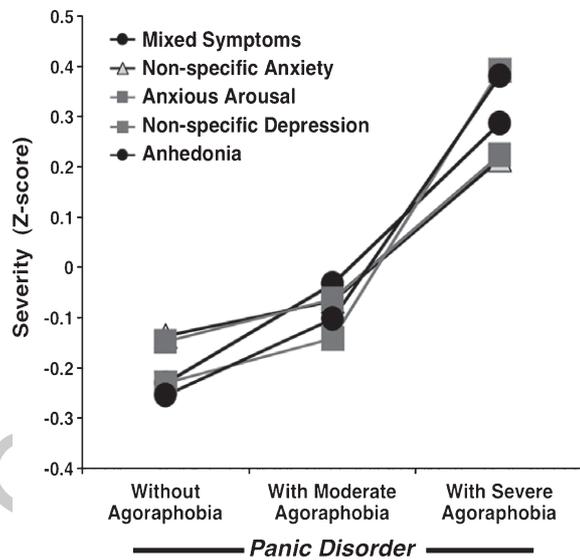


Fig. 5. Group means (standardized across participants) on the subscales of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1991) showing increasing broad negative affectivity with more generalized situational apprehension and avoidance within panic disorder.

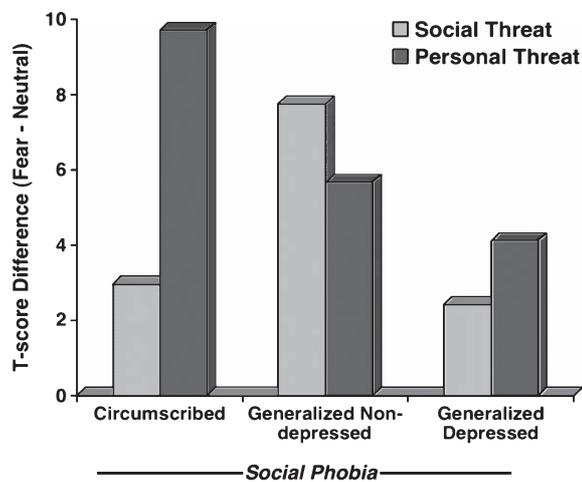


Fig. 6. Mean fear potentiation of startle reflexes (startle response magnitude during threat minus neutral imagery) during standard social threat as well as personal threat imagery for controls and patients with principal social phobia limited to performance situations, social phobia generalized to routine interaction as well as performance situations, and generalized social phobia patients with comorbid depression.

tle potentiation shows a clear covariation with principal diagnosis, paralleling factor analytic studies—greater for specific fear disorders, more blunted for disorders

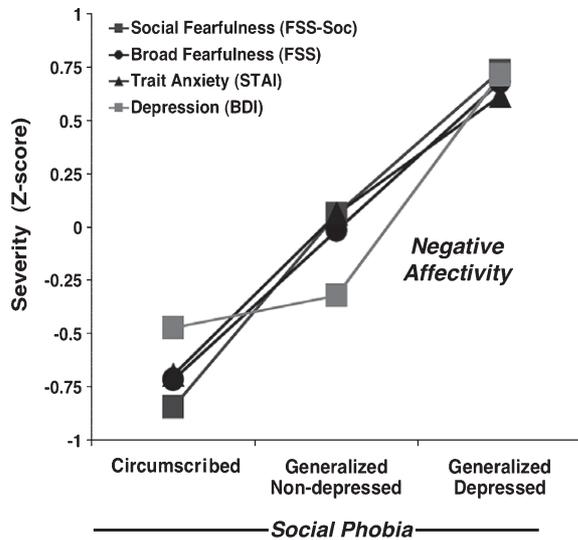


Fig. 7. Group means (standardized across participants) on the social fear subscale of the Fear Survey Schedule (FSS) (Wolpe et al., 1964), total fearfulness score of FSS, trait form of the STAI (Spielberger et al., 1983), and total BDI score (Beck et al., 1996) showing increased broad comorbidity from social phobia circumscribed to performance situations, social phobia generalized to routine interaction as well as performance situations, and finally the most extreme symptoms in generalized social phobia patients with comorbid depression.

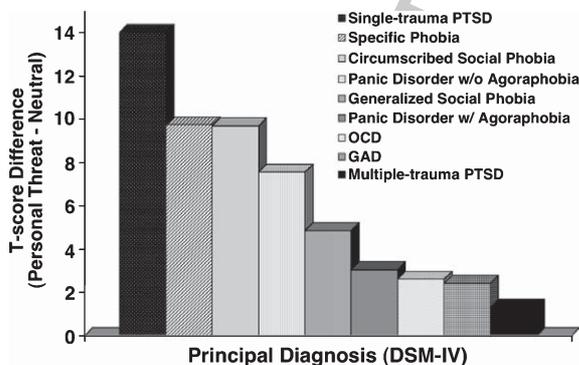


Fig. 8. Mean fear potentiation of startle reflexes (startle response magnitude during personal threat minus neutral imagery) for patients by principal disorder (OCD = obsessive compulsive disorder; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder) as determined with the Anxiety Disorders Interview Schedule for DSM-IV (Brown et al., 1994), arranged in order of decreasing response magnitude. Adapted from McTeague & Lang, 2012.

of anxious-misery—it is also clear that this is largely independent of principal diagnosis. PTSD patients illustrate this fact most dramatically: Depending on trauma frequency (and associated negative affectiv-

ity), PTSD patients are located at each extreme of the startle/anxiety spectrum—despite uniformly high ratings of fear intensity (negative arousal) during imagery that do not systematically differ across the anxiety disorders.

Overall, our research has defined several related factors that covary with increasingly blunted fear/startle potentiation, including higher scores on questionnaire measures of *negative affectivity*, reports of more frequent lifetime stress events, greater disorder chronicity, and increased comorbidity of depression and additional anxiety disorders (Lang & McTeague, 2009, 2011; McTeague, et al., 2009, 2010, 2011). Given the considerable evidence that potentiation is mediated by fear/defense circuit activation (with final projections from amygdala to the brainstem reflex pathway), it is suggested that these factors are associated with a fundamental, progressively more severe dysregulation of this neural network.

## 5. The fear/defense circuit: Neural imaging studies of anxiety disorder and depression

There is considerable neural imaging support for the view that the fear/defense circuit activated in normal fear conditioning is implicated in the pathophysiology of the anxiety disorders (e.g., Rauch et al., 2003). In their meta-analysis of neural imaging experiments across three anxiety disorders (social phobia, specific phobia, and PTSD), Etkin and Wager (2007) reported that “any of the three disorders consistently showed greater activity than matched comparison subjects in the amygdala and insula, structures linked to negative emotional responses” (p. 1476). Interestingly, they also found that activation of these structures was more reliable for specific and social phobia than for PTSD. This finding is consonant with the startle data presented here, as the PTSD sample could well have included patients with multiple trauma, greater comorbidity, and higher scores on trait negative questionnaires. So-called “pure” samples of specific DSM diagnosis are difficult to recruit, and critical moderating variables (e.g., comorbidity, chronicity, severity, and lifetime stress) are characteristic of the majority of treatment-seeking patients.

Functional MRI studies of depression are highly varied, and have rarely involved the narrative imagery procedure used in the startle research. Neural activity when processing happy and sad stimuli, however,

has often been assessed, including studies utilizing words (Canli et al., 2004), facial expressions (e.g., Gotlib et al., 2005; Lawrence et al., 2004; Surguladze et al., 2005), and memory prompts (Keedwell et al., 2005). In a meta-analysis that included these and other studies (Fitzgerald et al., 2008) the most consistently identified regions differentiating between depressed and non-depressed participants included areas of the medial and inferior prefrontal cortex, anterior cingulate, insula, superior temporal gyrus, and basal ganglia, although limited overlap across studies was also noted. Functional connectivity studies have investigated circuit activation in both resting state and during emotional challenges in depressed patients, reporting either heightened or attenuated circuit connectivity. In the resting state, for instance, both increased and decreased connectivity in core regions including the medial and dorsolateral prefrontal cortex (mPFC and dlPFC), the anterior cingulate and thalamus have been reported (Hasler & Northoff, 2011), with depressed patients showing heightened connectivity between the amygdala and hippocampus when encoding unpleasant pictures (Hamilton & Gotlib, 2008), but reduced connectivity between the amygdala and the anterior cingulate cortex (Anand et al., 2005).

Several leading investigators (e.g., Mayberg, 2007; Siegle et al., 2006; Victor et al., 2010) have focused on neural changes subsequent to treatment intervention. In general, these researchers agree that mood disorders are characterized by functional impairment in a system “that links the medial prefrontal cortex and a few related cortical areas to the amygdala, the ventral striatum and pallidum, the medial thalamus, the hypothalamus, and the periaqueductal gray and other parts of the brainstem” (Price & Drevets, 2010; see also Mayberg, 2003), structures also highlighted in animals studies of fear and appetitive motivation. Interestingly, Siegle et al., (2006) studied depressed individuals responding to masked emotional word stimuli and found that patients with attenuated amygdala activation at a pre-testing showed less improvement following cognitive-behavioral therapy—a finding consistent with the hypothesis that the amygdala is dysregulated in the more severely depressed and related to poorer treatment prognosis.

One view is that the symptoms of mood disorder are consequent on a failure of frontal cortical areas (or the subgenual cingulate gyrus) to inhibit a hyperactive

limbic system (e.g., amygdala); although an alternative hypothesis, prompted using deep brain stimulation as a treatment modality (Giacobbe et al., 2009), is that depressed mood is related to decreased activation in the ventral striatum/nucleus accumbens.

Importantly, abnormal activation or connectivity involving amygdala, the insula, the medial prefrontal cortex, and the nucleus accumbens (NAc), have been implicated in previous studies of depressed patients—as well as anxiety patients (Ressler & Mayberg, 2007). Furthermore, activation and connectivity patterns have been shown to vary as a function of phenotypic variants (Savitz & Drevets, 2009a, b).

An important focus of our own program of fMRI research has been to specify the neural correlates of emotional imagery, first in healthy normal participants and subsequently, in anxious and depressed individuals (e.g., Sabatinelli et al., 2006; Costa et al., 2010). In these studies, brief texts describing survival threat (e.g., an auto accident), animal attacks, contamination (e.g., a drunk vomits on your hand), erotic content (e.g., sexual encounters), scenes of joy (e.g., winning a lottery) and quotidian neutral scenes (e.g., doing laundry) are read and then imagined vividly for 12 s. The extent and temporal course of BOLD activity in the amygdala during a 12 s period involving pleasant, neutral, or unpleasant imagery are illustrated in Fig. 9: Imagining either pleasant or unpleasant events significantly increases amygdala activation, with little difference between the two emotional contents.

On the other hand, imagining pleasant scenes prompts unique increases in functional activity of both the nucleus accumbens and the medial prefrontal cortex activity (Fig. 10 top panel), whereas a dramatic reduction in regional blood flow during unpleasant imagery is found. When scripts are ranked by rated pleasure (Fig. 10, bottom panel), a strong linear relationship is found between pleasantness and functional activity for both mPFC ( $r=0.82$ ) and NAc ( $r=0.75$ ) such that there is a significant increase when imagining the most pleasant contents, and a significant decrease when imagining the most unpleasant contents. Because hemodynamic measures are thought to reflect both excitatory and inhibitory processes (Logothetis, 2008), the significant decrease in BOLD activity could indicate inhibition of the appetitive system in aversive arousal, permitting measurement of the reciprocal activation of a defense circuit. We have also found these same modulatory patterns in amygdala,

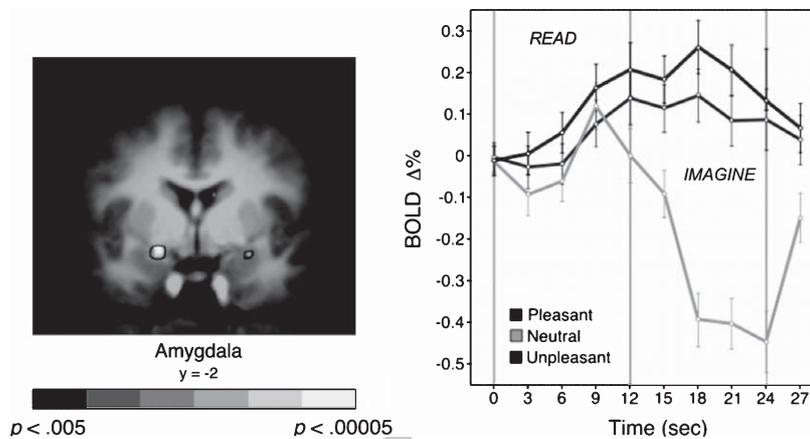


Fig. 9. Left panel. Increased activation in amygdala was observed for both pleasant and unpleasant compared to neutral imagery. Right panel. Mean event-related bold signal change (percent) in the amygdala during read (12 seconds) and imagery (12 seconds) of neutral, pleasant, and unpleasant narratives. Error bars represent 95% confidence intervals (Loftus & Masson, 1994). Adapted from Costa and colleagues (2010).

mPFC and NAc during emotional picture perception (Sabatinelli et al., 2007)—findings broadly consistent with appetitive and defensive circuitry identified in animal research (e.g., Baxter and Murray, 2002; Davis, 2000)

In a recent experiment using the same imagery procedure, we studied student volunteers selected on the basis of the Beck Depression Inventory-II (Beck et al., 1996; BDI-II). For the Low-BDI group ( $N = 16$ ), scores were well within the normal range (mean = 4.6; for the High-BDI ( $N = 15$ ) group, scores were in the range of clinical significance (mean = 24.9; range = 17–42). The High-BDI group also endorsed symptom elevations on the Mood and Anxiety Symptom Questionnaire (MASQ, Watson & Clark, 1991)—Depression, GDD  $M = 32.1$ ; anhedonia, AD  $M = 66.9$ —and on the Spielberger Trait Anxiety Inventory (Spielberger et al., 1983),  $M = 51.5$ . Of most interest in this pilot study were significant differences in functional activity in the amygdala for the two groups during unpleasant imagery (Fig. 11): Whereas the Low-BDI group showed the same amygdala enhancement when imagining unpleasant, compared to neutral scenes observed in our previous study of unselected college students (Costa et al., 2010), the depressed group (High-BDI) failed to show heightened amygdala activity when imagining aversive events. While these findings are certainly preliminary, they suggest a possible circuit dysregulation involving the amygdala during fear challenges in individuals high in depression/anxious misery.

## 6. Directions for future research

### 6.1. Dimensional diagnosis: Measuring fear/defense circuit activation across the anxiety spectrum

Extensive research demonstrates that the brain's fear defense circuit determines startle potentiation (mediated penultimately by projections from the central nucleus of the amygdala). Thus, the research reviewed here encourages the conclusion that blunted startle effects in anxiety spectrum patients are determined by brain circuit dysregulation and maladaptive brain plasticity. The findings obtained both across and within diagnoses suggest, furthermore, that anxiety pathology may be defined by a dimension of fear/defense circuit function. At one extreme are patients whose motivational circuitry is hyper-reactive to specific fear cues; at the other extreme are more chronic, symptomatically more severe patients with high comorbidity (co-active depression and other anxiety disorders) in which the fear circuit is compromised, and fails to mediate defensive reflexes that normally occur in the context of threat. Clearly, the next step in this research (consistent with the NIMH RDoC initiative) is to directly assess circuit function across the broad spectrum of anxiety disorder pathology—to measure fMRI activation patterns in the relevant brain structures and their connectivity during fear and non-fear imagery—and test the dimensional hypothesis prompted by the startle findings.

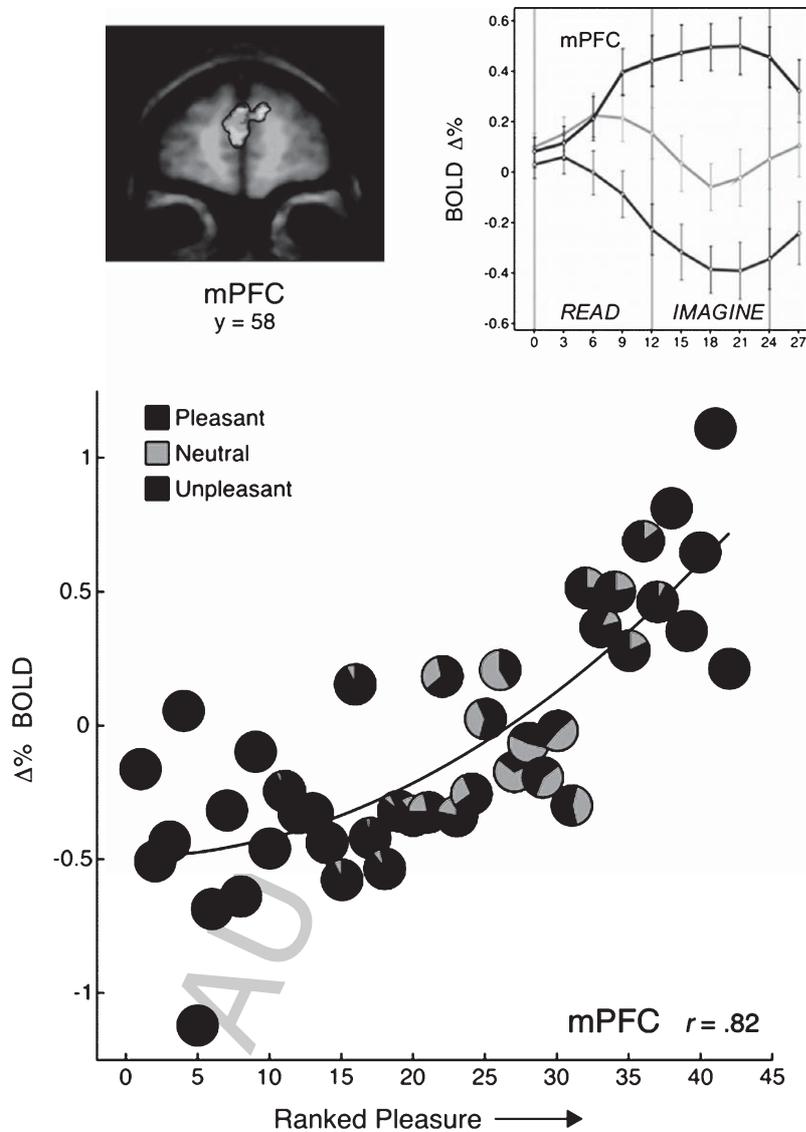


Fig. 10. Top left panel. Increased activation in mPFC was observed for pleasant compared to neutral imagery. Top right panel. Mean event-related bold signal change (percent) in the amygdala during read (12 seconds) and imagery (12 seconds) of neutral, pleasant, and unpleasant narratives. Error bars represent 95% confidence intervals (Loftus & Masson, 1994). Bottom panel. Scenes were rank ordered by each participant's pleasure ratings and plotted against the mean signal change in mPFC at each rank. Pie charts depict the proportion of the a priori selected pleasant, neutral, and unpleasant texts at each rank (based on ANET standardized ratings; Bradley & Lang, 2007). Adapted from Costa and colleagues (2010).

The factors determining the apparent fear circuit dysfunction are currently unknown. However, two broad hypotheses merit consideration. Dysregulation may be a consequence of cognitive processes. For example, severely distressed patients may have learned to dial-down their emotional response to memorial cues, perhaps employing strategies described in the

emotion regulation literature, “attention switching”, alterations in working memory, or reappraisal, that might be reflected in activation differences in pre-frontal or cingulate sites (e.g., Ochsner and Gross, 2005). On the other hand, patients showing the greatest reflex blunting are characterized by a history of persistent lifetime stress, reflected in repeated negative

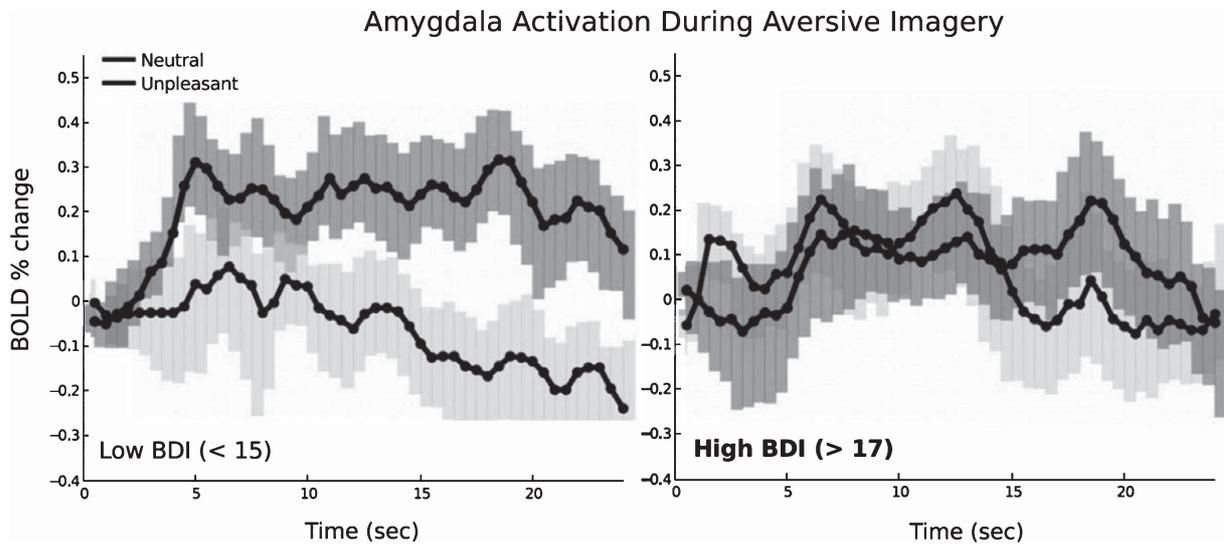


Fig. 11. Mean event-related bold signal change (percent) in the amygdala during read (12 seconds) and imagery (12 seconds) of neutral and unpleasant narratives for participants low and high in depression as indicated on the BDI (Beck et al., 1996). Error bars represent 95% confidence intervals (Loftus & Masson, 1994). Adapted from Costa, McTeague and colleagues (2010).

life events and/or multiple trauma experiences over many years, often beginning with childhood abuse. These findings suggest that sustained stress compromises normal functioning of the brain's fear/defense circuit, resulting in motor retardation, ineffective coping, and a diminished reflex response.

Research with animals lends support to this sustained stress view, as prolonged aversive stress is known to broadly suppress defensive reactivity (e.g. Rygula et al., 2005). In a study by Chalmers et al. (1974), for instance, startle reflexes in rats were not potentiated (relative to controls) and general activity significantly diminished for animals repeatedly exposed to intense, inescapable shock. Importantly, marked differences in reactivity have been found depending on the duration of stress. Thus, animals showed hyperarousal following a "resident intruder" stressor presented over a short period, whereas long duration exposure resulted in depression-like symptoms and suppressed activity (Avgustinovich et al., 2005). Radley et al. (2005) suggest, furthermore, that prolonged stress results in abnormal changes in brain plasticity in both animals and humans which impairs the ability to regulate and respond to subsequent stressors. Finally, genetic factors are probably involved, conferring greater vulnerability in some individuals that leads to circuit dysregulation and impaired coping (Uchida et al., 2010).

#### 6.1.1. Modifying emotional circuits using real-time fMRI feedback.

Technical advances in functional MRI recording now permit the near real-time acquisition of BOLD activity. Taking advantage of this capability, investigators have found that participants receiving real-time feedback learn to enhance BOLD activity in specific, pre-selected brain regions, subsequently reporting changes in cognitive and motor performance (deCharms et al., 2004; Posse et al., 2001), pain perception (deCharms et al., 2005), and language processing (Rota et al., 2009). In an initial study relevant to the brain's emotional circuitry, Birbaumer and colleagues demonstrated that healthy participants could use a thermometer-like feedback display of BOLD activity in learning to enhance activation of the anterior insula—a structure associated with affect and increased autonomic reactivity. It was furthermore observed that participants who were successful at this feedback task subsequently reported greater experienced affect when viewing pictures with emotional content in a free-viewing context (Caria et al., 2010). In subsequent studies this group of investigators has explored the use of feedback in modulating and classifying emotional imagery (Sitaram et al., 2011).

In consideration of these advances, we are developing a fMRI feedback methodology that could be used

as an adjunct tool to explore fear/defense circuit differences associated with the imagery processing deficits found in severe, comorbid anxiety patients. Real-time fMRI represents a new approach to circuit analysis in that a specified neural region—presumed to be part of the brain's motivational circuitry—can be itself manipulated as an independent variable, and dependent activation of hypothetically related downstream and upstream brain regions measured. In this sense, the use of structure-specific neurofeedback activation is analogous to stimulating an implanted electrode at a target site in an animal's brain and observing its efferent/afferent effects at recording electrodes implanted in other brain locations.

A first step in this effort could be to determine if the appetitive circuit activated in emotional imagery (Costa et al., 2010) can be modulated with feedback training. For example, the feedback thermometer could display BOLD reactivity in medial prefrontal cortex, testing whether learned enhancement of this signal prompts greater activation of amygdala and nucleus accumbens, components of the reward circuit described in the animal literature (Ambroggi et al., 2008; Mahler & Berridge, 2009; McGinty & Grace, 2008; 2009)—and here, potentially yielding causal information regarding circuit connections in the human brain. The fear/defense circuit can be similarly explored; in which case, for example, enhancing medial prefrontal cortex would be expected to reduce rather than augment reactivity in unpleasant/threat imagery.

The translational relevance of this strategy for understanding differences among anxiety patients is straightforward. First, it is a methodology that can be used to directly test hypothesized differences in motivational circuit patterns of activation and connectivity, potentially providing clear diagnostic bio-markers that more objectively measure dimensional differences in the anxiety spectrum. Second, considering the deficit in imagery processing found in chronic, comorbid patients, it could serve as an adjunctive treatment modality that increases circuit engagement in the imagery task, and thus improves the effectiveness of cognitive behavioral therapies (such as prolonged exposure for PTSD). Third, real-time fMRI feedback could be used to enhance appetitive/reward circuit activation in the context of positive affective cues, with potential application in the treatment of anhedonic and depressed patients.

## 7. Summary and conclusions

The research considered and proposed here is aimed at the development of biologically based measures that discriminate meaningfully among anxiety spectrum patients. The work is consistent with the RDoC program initiated by the National Institute of Mental Health (Insel et al., 2010), intending to encourage development of more objective ways to classify anxiety disorders that potentially have greater diagnostic specificity, prognostic significance, and more explicit treatment relevance.

Both factor analytic studies of anxiety spectrum patterns and genetic research suggest that anxiety disorders are distributed along a dimension of pathology extending from patients that show focal, exaggerated “fear” reactions (e.g., specific phobia; social performance anxiety) to patients with more generalized anxiety and mood symptoms, disorders of “anxious misery” (e.g. panic disorder with agoraphobia, generalized anxiety disorder). Our current studies provide strong evidence that an objective reflex measure—the startle response—varies along this dimension across the anxiety spectrum. That is, when fearful memories are evoked and probed with a brief acoustic stimulus, an exaggerated (potentiated) reflex is obtained in patients with focal fear disorders; however, this reaction is significantly blunted in patients with disorders classified as “anxious misery”. Importantly, the startle measure is also sensitive to this dimension within disorders. That is, as principal disorders are increasingly accompanied by more generalized symptoms, and mood and anxiety comorbidities, the startle probe reflex is progressively more impaired.

Research with both animals and human participants confirms that startle potentiation is mediated by activation of the brain's fear/defense circuit, prompting the hypothesis that motivational circuits are compromised, increasingly dysregulated in patients in which the “anxious misery” symptom complex has greater prominence. Our preliminary fMRI studies encourage us in this view, and a broad study of the full range of anxiety pathology is planned in which we will analyze both appetitive and fear/defense circuit activation patterns, and directly test their relationship to startle reactivity over the anxiety spectrum. In this effort, we will also employ real-time fMRI feedback to modulate motivational circuits, with the aim of assessing dimensional differences in circuit connectivity, and

evaluate this procedure as a method for up-regulating circuit function and increasing imagery engagement in patients showing blunted affect. In summary, the proposed research is an effort to develop objective biomarkers that meaningfully discriminate among anxiety patients, assessing severity of disorder, providing better prognostic data, and define more productive targets for treatment.

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