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Research report

Elevated amygdala activity during reappraisal anticipation predicts anxiety in avoidant personality disorder

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ABSTRACT

Background: Avoidant personality disorder is characterized by pervasive anxiety, fear of criticism, disapproval, and rejection, particularly in anticipation of exposure to social situations. An important but underexplored question concerns whether anxiety in avoidant patients is associated with an impaired ability to engage emotion regulatory strategies in anticipation of and during appraisal of negative social stimuli.

Methods: We examined the use of an adaptive emotion regulation strategy, cognitive reappraisal, in avoidant patients. In addition to assessing individual differences in state and trait anxiety levels, self-reported affect as well as measures of neural activity were compared between 17 avoidant patients and 21 healthy control participants both in anticipation of and during performance of a reappraisal task.

Results: Avoidant patients showed greater state and trait-related anxiety relative to healthy participants. In addition, relative to healthy participants, avoidant patients showed pronounced amygdala hyper-reactivity during reappraisal anticipation, and this hyper-reactivity effect was positively associated with increasing self-reported anxiety levels.

Limitations: Our finding of exaggerated amygdala activity during reappraisal anticipation could reflect anxiety about the impending need to reappraise, anxiety about the certainty of an upcoming negative image, or anxiety relating to anticipated scrutiny of task responses by the experimenters. While we believe that all of these possibilities are consistent with the phenomenology of avoidant personality disorder, future research may clarify this ambiguity.

Conclusions: These results suggest that amygdala reactivity in anticipation of receiving negative social information may represent a key component of the neural mechanisms underlying the heightened anxiety present in avoidant patients.

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1. Introduction

Avoidant personality disorder seriously and chronically impairs interpersonal and occupational functioning and is among the most prevalent personality disorders (Skodol et al., 2002; Torgersen et al., 2001). It is characterized by a pervasive pattern of avoiding interpersonal contact because of fears of criticism, disapproval or rejection. This leads to serious limitations in the ability to function in occupational settings and severely circumscribed interpersonal relationships. In particular, the prospect and anticipation of exposure to social situations generates high levels of anxiety in individuals with avoidant personality disorder (Hummelen et al., 2007).

Although a considerable body of work has addressed the phenomenology of avoidant personality disorder (Sanislow et al., 2012), few studies have probed its underlying neurobiology and in particular the neural mechanisms associated with the anxiety response and those that serve to regulate emotion. To our knowledge, the only

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published functional neuroimaging study of avoidant patients was a study by our group that examined the neural correlates of an implicit emotion regulatory mechanism, habituation (Koenigsberg et al., 2014). We found that avoidant patients did not habituate to repeated negative image presentation and did not increase dorsal anterior cingulate cortex activity, associated with cognitive control and reduced affective instability, to the level of healthy volunteers, providing preliminary evidence that avoidant patients show anomalous implicit emotion regulation.

Another adaptive and commonly employed emotion regulatory mechanism is cognitive reappraisal (Gross, 1998). Unlike habituation, cognitive reappraisal is a deliberate and voluntary mechanism. It entails cognitively reframing an emotional stimulus so as to change one's response to it. In the case of an aversive situation, reappraisal can be used to render it less disturbing (Gross, 1998). Two commonly employed reappraisal tactics are situational reinterpretation and psychological distancing (McRae et al., 2012; Ochsner and Gross, 2008). In the former, a narrative is created for the aversive situation that portrays it more positively (e.g. a scene depicting a sickly looking man lying in a hospital bed is rendered less disturbing by imagining that he is beginning to respond to a highly effective treatment). In the latter, the individual adopts a perspective that fosters experiencing the situation as remote from the self (e.g. the emergency room physician employing clinical detachment to function effectively in the presence of disturbing stimuli).

Cognitive reappraisal and its neural correlates have been studied extensively in healthy populations (Buhle et al., 2014; Ochsner and Gross, 2008; Ochsner et al., 2012). This work has identified the regions consistently recruited by reappraisal (i.e. associated with emotion *regulation*), including those associated with selective attention and working memory (e.g. dorsal anterior cingulate cortex and dorsolateral prefrontal cortex), mental state attribution (e.g. medial prefrontal cortex), and response selection and inhibition (particularly ventrolateral prefrontal cortex) (Ochsner et al., 2012). This reappraisal-related activity has been shown to modulate the activity of subcortical appraisal regions (i.e. associated with emotion *reactivity*), most crucially the amygdala (Wager et al., 2008), which has been associated with detection of arousing and potentially threatening stimuli (Buhle et al., 2014; LeDoux, 2000; Ochsner et al., 2012).

While no studies have examined the neural mechanisms of reappraisal anticipation or implementation in avoidant personality disorder, aberrant patterns of activity during reappraisal—particularly involving hyperactivity of the amygdala—have been noted in patients with other mood and anxiety disorders such as major depression (Johnstone et al., 2007), borderline personality disorder (Koenigsberg et al., 2009; Schulze et al., 2011), and social anxiety disorder (Goldin et al., 2009a; Goldin et al., 2009b; Klumpp et al., 2010; Marazziti et al., 2014) relative to healthy controls. Variable, though often substantial, comorbidity between social anxiety disorder (also known as generalized social phobia) and avoidant personality disorder has been reported (Reich, 2009), though avoidant personality disorder is thought to be the more serious of the two disorders in terms of functional impairment and symptom severity (Marques et al., 2012; Reich, 2009; Rettew, 2000; Sanislow et al., 2012). Importantly, in addition to during stimulus presentation, amygdala activity has been associated with anticipation of aversive events in social anxiety disorder patients (Boehme et al., 2014; Lorberbaum et al., 2004) as well as in healthy participants (Herwig et al., 2007; Ueda et al., 2003), though the effects in social anxiety disorder patients have been shown to be significantly greater than those shown by healthy controls (Boehme et al., 2014; Lorberbaum et al., 2004).

Avoidance of social situations, which is the hallmark of avoidant personality disorder, is predicated upon anticipatory anxiety (Hummelen et al., 2007). We therefore examined neural activity during the period when participants anticipated the reappraisal task, a situation in which they would expect their performance to be judged by the experimenters. Because the anxiety in avoidant personality disorder is associated with fears of public shame, disapproval and social rejection, it generalizes beyond previously used categories of stimuli such as fear of angry or contemptuous faces. We therefore sought to examine cognitive reappraisal in avoidant patients in response to images depicting an array of aversive interpersonal situations including loss, tragedy, and hostility. The neural correlates of anticipating reappraisal as well as reacting to and reappraising aversive social images were compared in avoidant patients and healthy participants using functional magnetic resonance imaging (fMRI). We predicted that avoidant patients would show exaggerated anxiety relative to healthy participants as measured by behavioral self-reports as well as elevated reactivity in the amygdala, particularly during anticipation of reappraisal.

2. Methods

2.1. Participants

23 avoidant and 24 healthy participants were recruited from outpatient clinics at the Mount Sinai Medical Center and the James J Peters VA Medical Center in New York City, as well as from newspaper and online advertisements. All participants provided written informed consent to participate after all procedures were fully explained according to the regulations of the Institutional Review Board at the Icahn School of Medicine at Mount Sinai. Six avoidant participants and 3 healthy participants were excluded for technical reasons (shown in Supplementary material). Thus, the present results reflect data from 17 avoidant and 21 healthy participants. Sample characteristics are given in Table 1.

2.2. Screening and sample comorbidity

Participants in the avoidant group met DSM-IV criteria for avoidant personality disorder but not criteria for borderline or schizotypal personality disorder. Participants were excluded if they met DSM-IV criteria for past or present posttraumatic stress disorder, bipolar I disorder, schizoaffective disorder, substance dependence, organic mental syndromes, head trauma, central nervous system neurological disease, seizure disorder, substance abuse disorder in the previous 6 months, or current major depressive disorder. Participants with significant medical illness, contraindications to fMRI, pregnant women, and those with current suicidal ideation were excluded. Participants had to be free of psychotropic

Table 1
Sample characteristics.

	Avoidant group	Healthy group	Avoidant group versus healthy group
N	17	21	
Mean age	29.59 (7.16)	29.00 (6.71)	$t(36)=0.26$, n.s.
Gender (F/M)	8/9	11/10	$\chi^2=0.74$, n.s.
STAI state	35.60 (9.61)	26.53 (3.78)	$t(30)=3.22$*, $d=1.18$
STAI trait	39.35 (8.45)	28.74 (5.68)	$t(34)=4.25$**, $d=1.46$
HAM-D	4.20 (3.03)	2.08 (3.63)	$t(25)=1.61$, n.s.

Standard deviations are given in parentheses.

* $p<0.01$, two-tailed.

** $p<0.001$, two-tailed.