The Aftermath of Affective Stimuli: Evidence from fMRI Recorded Amygdala and Hippocampal Activity in Generalized Anxiety Disorder

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Introduction

Generalized anxiety disorder (GAD) patients exhibit heightened anticipatory amygdala activity before presentations of affective pictures (Nitschke et al., 2009) and facilitated memory for threat stimuli (Friedman, Thayer, & Borkovec, 2000). Worrying (defining feature of GAD) also promotes the recurrence of distressing thoughts following exposure to aversive information (Wells & Papageorgiou, 1995).

Amygdala hypoactivity to aversive pictures and sustained pupil hyporesponsivity following affective stimulus presentations characterize GAD patients’ chronic worries (Oathes et al., 2007; Oathes, Siegle, & Ray, submitted). These data are consistent with a theory that avoidance of aversive information is instrumental in the maintenance of anxiety in GAD (Borkovec et al., 2004). The current study examines effects of valence and attention focus (subjective mood or picture affectivity ratings) on neural activity in the amygdala and hippocampus in GAD patients following presentations of affective pictures.

Methods

13 GAD patients (2 male, non-medicated, no other current or past Axis I disorders); 13 Controls (no current or past Axis I disorders) matched gender and age. Participants were administered self-report questionnaires before the scan including a measure of discomfort with uncertainty (Intolerance of Uncertainty) and a questionnaire assessing chronic uncontrollable worry symptoms (Penn State Worry Questionnaire).

Event-related paradigm based on our previous work (Nitschke et al., 2009) provides a 1-ssec warning cue (X or O) before a 1-ssec affective picture presentation (negative or neutral) from the IAPS set (variable ITIs between events) followed by a 3-ssec rating period. On each trial, participants rated either the picture presented or their mood on a -4 (unpleasant) to +4 (pleasant) Likert-type scale.

MRI acquisition & analysis: GE 3.0T scanner. Anatomical scans: Hi-resolution T1- weighted 3D SPGR (TR/TE=8.9,1.8ms), flip angle=30°, NEX=1, FOV=240mm, matrix=256x192, slice thickness/gap=1.20 mm, 124 slices). Functional scans: 30 sagittal T2*-weighted EPI slices (TR/TE=2000/30 ms, flip angle=90°, NEX=1, FOV=240mm, matrix=64x64, slice thickness/gap=4/0.5 mm, in-plane resolution=3.75 x 3.75 mm). Processing implemented via AFNI including image reconstruction, slice time correction, 6 parameter rigid-body motion correction, field map correction, and registered to Hi-res T1 scan for each subject which was warped (12 parameter affine) to MNI-152 brain (provided in AFNI with Talairach-Tournoux coords) using @auto_6c. Events were convolved with a canonical HRF (GAM) separately for valence (negative,neutral) and rating type (mood or picture rating) and beta weights from the GLM (3dDeconvolve) were converted to % signal change before being subjected to a group x x focus ANOVAs. Significant whole-brain effects and interactions at p<.005, uncorrected, were extracted (average % change over cluster per condition per subject) to provide bar graphs and text for correlations with trait measures of anxiety and depression.

Results

A Group x Focus x Valence (Negative, Neutral) interaction, F(1,24)=11.74, p=.006 in the Left Amygdala (Figure 1). Driven by a significant Attention Focus effect in Controls, F(12)=2.32, p=.038 but not in GAD patients, p=.34 (Figure 2).

For the Rating period following picture presentations, a Group (GAD,Control) x Valence x Rating (Picture Ratings) interaction was present in the Right Amygdala (Figure 1), driven by a significant Attention Focus effect in Controls, F(12)=2.32, p=.038 but not in GAD patients, p=.34 (Figure 2).

Instead, GAD patients showed hypoactivity in the amygdala to both types of ratings. Their hypoactivity to Mood Ratings was correlated with severity of chronic worry symptoms assessed by the PSWQ (Figure 3). Amygdala activity was not correlated with worry scores in Control participants.

Correlations with Hippocampal Response

In GAD patients, during Mood ratings following Neutral Pictures, hippocampal activity was associated with relatively fewer worry symptoms (Figure 6).

In Controls, during Mood ratings following Neutral Pictures, relatively more hippocampal activity was correlated with fewer symptoms of uncertainty intolerance (Figure 7).

Conclusions

-Differences between GAD and matched Control participants emerged in the aftermath of affective stimulus presentations in the right amygdala and left hippocampus.

-AMYDALA hyporesponsivity to pictures in GAD may indicate avoidance tendencies and the lack of responding to mood ratings was specifically associated with trait worry elevations. Hyporesponsivity in controls did not correlate with symptom scales but the same direction of activity in GAD patients had pathological correlates (worry severity and worry chronicity).

-In light of symptom correlates, there is evidence for avoidance tendencies in GAD patients (correlates of Hippocampus activity to Neutral Mood Ratings and Amygdala response to Mood Ratings). These correlates do not necessarily reflect directions of group difference in brain activity in the ROIs. Thus, a more comprehensive evaluation of related brain activity patterns is warranted.

-Future analyses will also evaluate predictors of the anxious response profile from anticipatory and picture period neural activity. Consequences of hippocampal and amygdala activity in memory performance will also be assessed with this data set.

References


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