

# Toward functional neurobehavioral assessment of mood and anxiety

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**Abstract**—Mood and anxiety disorders confer marked personal and fiscal cost. Current therapeutic efforts show only moderate efficacy, and little is known about the characteristics of those who respond to specific treatment regimens. The lack of objective descriptors of symptom severity and reliable predictors of illness outcome contributes to limited diagnostic and treatment success. Here, we have begun to develop a normative neurobehavioral database of responses to affective stimuli by combining functional magnetic resonance imaging (fMRI), with comprehensive behavioral assessment and quantitative analyses of neural responses to standard emotional cues. These data reveal robust and distinct neural patterns between two groups with similar low self-reported depression and anxiety, and one group with high depression and anxiety scores. This and related strategies may be used to identify covert phenotypes associated with psychiatric illness and resilience.

## I. INTRODUCTION

**A**NOMALOUS responses to emotional stimuli are prominently and differentially implicated in the pathophysiology of mood and anxiety disorders (e.g., [1-7]). For example, in studies examining neural activation to emotional cues, exaggerated responses in amygdala are consistently observed in individuals with post-traumatic stress disorder (PTSD), and subgenual cingulate cortex dysfunction is implicated in major depressive disorder (for reviews, see [8, 9]). However, current diagnostic and symptom assessments for these conditions rely on subjective self-report and the clinical judgment of trained assessors. We suggest that these tools may be supplemented and refined with neurobehavioral measures as objective metrics of mental health.

As a first step toward developing such neurobehavioral assessment tools, our broad hypothesis is that key aspects of affective dysfunction in mood and anxiety disorders may be objectively mapped onto neural activity observed during emotionally evocative tasks. To this end, we have begun to develop a large normative database of responses to affective stimuli by combining functional magnetic resonance imaging (fMRI) with comprehensive clinical and behavioral assessments to quantify normative neural responses to validated emotional cues. The approach is thus to reduce complex phenotypes in mood and anxiety disorders to simple coefficients associated with emotional functioning

using objective neural indices that can be characterized with reference to large normative datasets.

In the present analysis, we focus on neural regions and self-reported mood and anxiety symptoms reported in unselected control participants. In PTSD and other anxiety disorders, one of the most consistent neurobiological findings across a myriad of functional neuroimaging studies is *over-active* amygdala functioning during the processing of trauma-related cues [9]. That is, across emotional activation studies, symptom provocation studies, and fear-conditioning studies, individuals with PTSD and other anxiety disorders show hyperactivation of amygdala to trauma-related versus neutral or generally negative cues [10-14]. In individuals with major depression, normal, blunted, and exaggerated amygdala responses have all been reported in functional neuroimaging studies of emotional function [15-18]. One intriguing line of research suggests that in depression the duration of amygdala response to emotional stimuli may be perturbed in depression such that elevation in hemodynamic activity during exposure to negative words persists for an extended time [19, 20]. Thus, aberrations in amygdala and other neural responses to emotional stimuli have been shown to differentially characterize groups with mood and anxiety disorders (in particular, depression and PTSD).

Based on these and other observations, we posit that fMRI combined with simple emotion provocation tasks and a large normative sample may identify potential tools for objectively measuring emotional function and assessing the integrity of well-defined neural pathways in depression, anxiety and other psychopathologies [8, 21]. Toward this end, our primary goals were first, to begin a large normative dataset of normative fMRI responses to emotional stimuli against which impairments might be compared; and second to assess whether analyses of fMRI imaging during passive viewing of standard emotional pictures might be sufficient to identify mood/anxiety “types” that may not be accessible by behavior or self-report alone.

## II. METHODS

### A. Overview

Healthy subjects participated in fMRI scanning during passive viewing of emotional images drawn from the International Affective Picture System (IAPS; [22]). Participants also completed an extensive battery of self-report measures assessing a range of mood and anxiety symptoms and trait characteristics.

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Self-reported depression and neural activity in regions-of-interest showing responses to emotional stimuli were subjected to k-means clustering analysis seeking two, three, or four cluster solutions. Members of clusters with optimal silhouette scores were examined to identify subject characteristics that differentiated clusters.

### B. Participants

Fifty male and female participants recruited from the Houston metropolitan area took part in the study. Exclusion criteria included left-handedness, current psychiatric treatment, and history of major medical illness or head trauma. In accord with Institutional Review Board guidelines, written informed consent was obtained prior to begging the study. All participants were compensated \$10/hr for the behavioral assessments, and \$20 for the scanning portion of the study. Participant characteristics and distribution of self-reported depression scores are reported below (**Table 1** and **Figure 1**).

TABLE 1  
PARTICIPANT CHARACTERISTICS

Variable	Mean
# female	24
# Caucasian	32
Average IQ*	118
Average age (years)	28
Average education (years)	18

\*Wechsler Test of Adult Reading (WTAR)

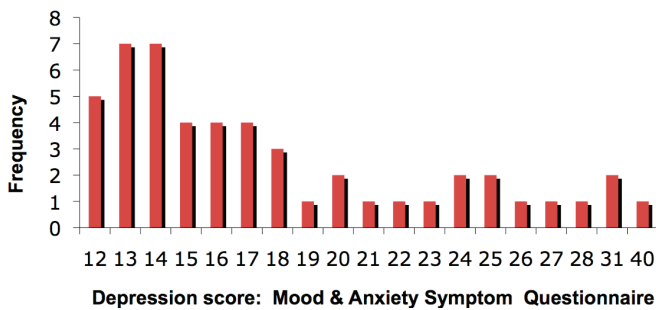


Fig. 1. Frequency distribution of depression symptoms

### C. Task

As illustrated in **Figure 2**, fMRI scanning was performed while participants viewed a series of individually presented images, a third of which were positive emotional valence, a third of which were negative valence, and a third of which were neutral. Participants were asked to simply relax and view the images. Presentation of images from the IAPS occurred in two rounds repeating 216 total images (72 each: positive, negative, and neutral). Stimuli were presented for 768 ms (followed by 768 ms blank), in 24 blocks of 9 images of the same valence category. The orders of images and of valence categories were randomized to produce a unique sequence for each subject.



Fig. 2. Schematic depiction of emotional picture viewing task.

### D. fMRI data acquisition and reduction

All scans were performed on a Siemens 3.0 Tesla Allegra scanner with standard imaging parameters. Initial high-resolution T1-weighted scans were acquired using an MP-RAGE sequence (Siemens). Continuous whole brain imaging was performed as participants engaged in the picture viewing. For measurement of the blood oxygenation level-dependent (BOLD) effect [23-25], functional run details were as follows: echo-planar imaging, gradient recalled echo; repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle = 90°; 64 x 64 x 64 matrix, 34 4mm axial slices acquired angled 30 degrees from the anteroposterior commissural line. Scanning yielded functional 3.44 mm x 3.44 mm x 4.0 mm voxels.

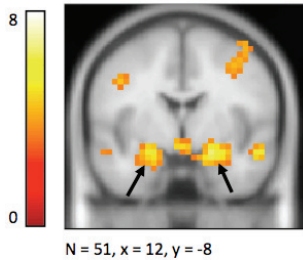
Data reduction was performed using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>). Motion correction to the first functional scan was performed using a six-parameter rigid-body transformation within subjects [26]. The average of the motion-corrected images was co-registered to each individual's structural MRI using a 12-parameter affine transformation. Slice timing artifact was corrected, and images were subsequently spatially normalized to the MNI template by applying a 12-parameter affine transformation, followed by a nonlinear warping using basis functions as recommended by Ashburner and Friston [27]. Finally, images were smoothed with an 8 mm isotropic Gaussian kernel and highpass filtered in the temporal domain (filter width 128s).

### E. General Linear Model and cluster analyses

Self-reported depression and neural activity in regions-of-interest showing responses to emotional stimuli (here, bilateral amygdala) were subjected to k-means clustering analysis seeking two, three, or four cluster solutions. Members of clusters with optimal silhouette scores were examined to identify subject characteristics that differentiated clusters.

The variables included in the cluster analysis were (i) individual subjects' z-scored beta values extracted from the bilateral amygdala region identified in whole brain GLM analyses of neural responses to negative images (**Figure 3**) and (ii) z-scored self-reported depression scores from the depression subscale of the Mood and Anxiety Symptom Questionnaire (MASQ; [28, 29]). K-means clustering was

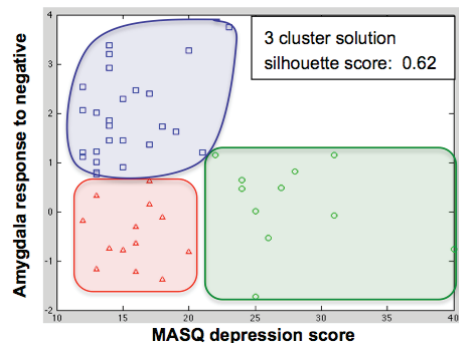
implemented in Matlab 7.5 with 1000 iterations, each with new initial centroids. The most repeated cluster groupings were extracted for further analysis. For each of the final clusters, overall silhouette scores and within cluster silhouette scores were obtained (squared Euclidean distance).



**Fig. 3. Regions identified in passive viewing of negative images used to select regions-of-interest and extract beta values for cluster analysis.** Whole brain GLM analyses identified bilateral amygdala response,  $p < .01$  FDR correction).

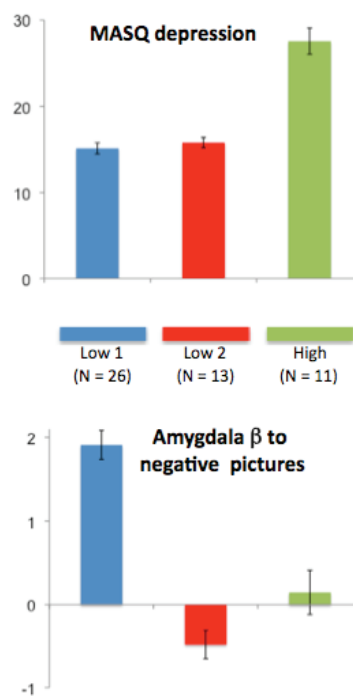
### III. RESULTS

A robust three cluster solution (silhouette score 0.62) was identified in these data, depicted in **Figure 4**. As illustrated here, the k-means algorithm assigned individuals Low and High Depression groups (mean MASQ depression 15.1 and 20.7, respectively). Within the Low Depression group, we observed further differentiation by distinct neural responses in bilateral amygdala to negative stimuli. The two Low Depression groups are subsequently referred to as “Low 1” and “Low 2”, respectively, and shaded in Blue and Red throughout the Results. The High Depression group is shaded in Green.



**Fig. 4. K-means cluster analysis with z-scored self-reported depression scores and amygdala responses to negative stimuli identifies robust 3 cluster solution.** The scatter plot shows individual subjects assigned to each of the three clusters: two low depression groups (Low 1 and Low 2) and one high depression group (High).

As illustrated in **Figure 5**, the two Low Depression groups did not differ in self-reported depression score. In marked contrast, these two Low Depression groups showed distinct neural responses such that the Low 1 group exhibited significantly greater neural responses to negative stimuli than the Low 2 group. The three groups did not differ in any demographic variables, including age, IQ, or gender (see **Table 2**).



**Fig. 5. The identified clusters differ on depression symptoms and neural activation to emotional stimuli.**

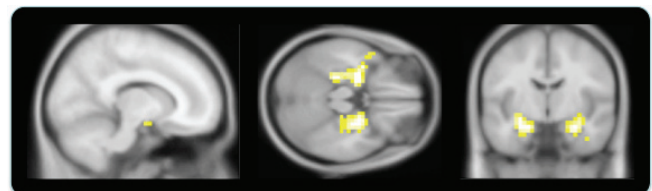
(Top) Mean self-reported depression reveals two non-different ( $p = 0.8$ ) Low depression groups, and a High depression group that differs from both Low groups ( $p < .0001$ ); depression subscale of the Mood and Anxiety Symptom Questionnaire.

(Bottom) Mean beta values to negative images in the identified bilateral amygdala region-of-interest show the two Low depression groups differ in neural responses to negative images (Low 1 vs Low 2,  $p < .0001$ ; Low 2 vs High,  $p = .05$ ).

TABLE II  
PARTICIPANT CHARACTERISTICS WITHIN EACH CLUSTER

	Low 1	Low 2	High
BDI depression	4.5	4.9	10.4
MASQ anxiety	15.2	15.0	20.7
MASQ anhedonia	45.9	49.8	63.2
age	29.9	25.5	26.3
IQ	118.8	116.6	116.3
% female	46%	46%	55%

Finally, post-hoc whole brain contrast analyses between Low Depression Group 1 and Low Depression Group 2 confirmed the neural differentiation in bilateral amygdala in these two groups (**Figure 6**).



**Fig. 6. Whole brain GLM comparison of Low Depression Group 1 > Low Depression Group 2 neural responses to negative images;** two-sample t-test;  $p < .01$ , FDR correction.

### IV. DISCUSSION

Using a simple emotional picture viewing task, mood symptom assessment, functional magnetic resonance imaging, and cluster analyses, we report (i) amygdala response to negative stimuli and (ii) a three cluster solution with self-reported depression and amygdala-based analyses. The three clusters comprised two low depression/anxiety groups and one high depression/anxiety group. The two low symptom groups were characterized by distinct and

differential neural responses to emotionally evocative stimuli. Quantifying neurobehavioral endophenotypes using standardized responses elicited in the context of well-characterized paradigms may aid in objective psychiatric assessment and quantification of therapeutic response. These data highlight the potential utility of imaging-based approaches to identify endophenotypes not accessible by behavior or self-report alone. That is, these data show we are able to identify robust neural patterns that are associated with mood and anxiety symptom severity, and that we can reduce multi-dimensional complex phenotypes to single metrics. In the long term, this and similar tasks may be used as functional assays targeting brain and emotional states associated with symptom severity, providing easy-to-implement assessments with prognostic utility and guiding novel biologically informed treatments.

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