

RUNNING HEAD: fMRI predicts recovery from depression

**fMRI Predicts Recovery in Cognitive Behavior Therapy for Unipolar Depression**

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### **Abstract**

**Objective.** 40-60% of unmedicated depressed individuals respond to Cognitive Behavior Therapy (CBT) in controlled treatment trials. We examined whether neural reactivity to emotional stimuli before treatment accounted for this variation.

**Method** 14 unmedicated depressed individuals and 21 controls were assessed with fMRI on a task sensitive to sustained emotional information processing. Afterwards, depressed participants completed 16 sessions of CBT.

**Results.** Participants with the lowest sustained subgenual cingulate cortex (BA25) and highest sustained amygdala reactivity to emotional stimuli displayed the strongest improvement in CBT.

**Conclusions.** Having disruptions of emotion regulation, which are targeted in CBT, may be key to recovering in this intervention.

## Introduction

Cognitive Behavioral Therapy (CBT) (1) is a common empirically supported intervention, effective for 40-60% of patients with unipolar depression (2). Knowing which patients are likely to benefit from CBT could increase the response rate and decrease costs by targeted referrals. CBT involves, among other skills, learning to interrupt automatic sustained emotional processing with controlled processing. As a preliminary step towards prediction, this study examined associations of pre-treatment neural substrates of sustained emotional processes such as elaboration, rumination, and regulation with recovery. Sustained emotional reactivity was examined because it is specifically addressed in CBT and because depressed individuals display increased and sustained reactivity in brain regions subserving emotional processing, particularly the amygdala (3-5). Unmedicated unipolar depressed patients entering CBT underwent functional magnetic resonance imaging (fMRI) during an emotional information processing task. Analyses identified brain regions where sustained reactivity to emotional information was associated with symptom change. Activity in these regions was then compared to healthy controls.

## Method

### Participants

Participants included 14 individuals with unipolar major depressive disorder, ages 23-55,  $M(SD)_{\text{age}}=45.21(9.3)$ ,  $M(SD)_{\text{Beck Depression Inventory (BDI)}}=24(11.7)$ , 7 male, 11 Caucasian, and 21 healthy controls (no current or historical Axis I disorder); 9 male, 12 Caucasian,  $M(SD)_{\text{age}}=31.3(8.6)$ ,  $M_{\text{BDI}}=3.7$ . Participants passed a cognitive screen, VIQ-equivalent  $> 90$ , and described no history of psychosis, manic or hypomanic episodes, no antidepressant use within two weeks of testing (six weeks for fluoxetine), and no health problems, eye problems, or

psychoactive drug or alcohol abuse in the past six months.

### **Procedure**

After signing IRB-approved consent forms, a diagnostic interview (6), vision test, and psychophysiological measures, participants underwent fMRI assessment<sup>1</sup>. In the scanner, participants rated the personal relevance of 60 emotional words (as in (3); 20 positive, 20 negative, 20 neutral: half normed and half idiosyncratically generated. Normed words were balanced for affective intensity, arousal, word length, and word frequency). Trials entailed a fixation cue (1s) followed by a word (200ms), followed by a mask (thirteen X's; 10.8s). Participants pushed buttons on a response box for whether each word was relevant, somewhat relevant, or not relevant to them, as quickly and accurately as possible. Stimuli were displayed in black on a white background via a back-projection screen (.88° visual angle). Mappings of buttons to responses were counterbalanced across participants.

Depressed participants then received sixteen sessions of CBT over 12 weeks following Beck's (1) guidelines. At each session, participants completed the Beck Depression Inventory II (BDI) to assess depressive severity.

### **Analytic approach**

To examine change in severity, not confounded by initial severity, residual change in depressive severity was computed from a regression of initial BDI scores on final BDI scores.

fMRI data were preprocessed via motion and outlier-correction, linear trend removal, temporal smoothing (5-point filter), linear cross-registration to a reference brain, and spatial smoothing (6mm FWHM). Whole-brain voxelwise regressions of residual severity on mean fMRI signal 6-10.5s following presentation of negative words minus a pre-stimulus baseline were used to detect

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<sup>1</sup> GE 3T, T2\*-weighted images depicting BOLD contrast; reverse spiral pulse sequence, TR=1500ms, TE=5ms, FOV=24cm, flip=60; 30 or 34 3.2mm slices parallel to the AC-PC line; 8 volumes per 12 second trial

regions in which activity was associated with recovery. Type I error was controlled by selecting only large clusters of significant voxels. To test *a priori* hypotheses, significant clusters in the amygdala (boundaries from (3); small-volume correction) were examined. Group differences were tested in identified regions via *a priori* contrasts on sustained activity and exploratory group x valence x scan mixed effects analyses using an AR1 covariance structure to account for temporal autocorrelation. Type 1 error was controlled for simple-effects tests via Bonferroni correction.

## Results

### CBT effects

CBT response was variable but generally successful, Completer M(SD) pre-treatment BDI=24.5(12.0), M(SD) post-treatment BDI=9.4(8.1), M(SD)change=15.1(11.8),  $t(13)=4.8$ ,  $p<.0005$ . Initial severity accounted for 13.7% of variation in final severity.

### Associations of activity with symptom change

Whole-brain analyses revealed only that decreased sustained activity to negative words in the subgenual cingulate cortex (BA25) was strongly associated with reduced severity following CBT (Figure 1A). BA25 activity accounted for 56.7% of variation above and beyond initial severity, total  $R^2=.65$ ,  $F(1,12)=22.4$ ,  $p<.0005$  and was unrelated to initial severity,  $R^2=.001$ ,  $p=.79$ .

Logistic regression further revealed that BA25 activity predicted recovery defined as  $BDI_{final} < 8$ ,  $X^2(1)=5.3$ ,  $p=.02$ ; 7/9 patients were correctly predicted to recover, and 4/5 patients were correctly predicted to not recover. When the one outlier was removed, pre-treatment BA25 activity accounted for nearly all variation in response to CBT,  $R^2=.91$ ,  $F(1,11)=124.9$ ,  $p<.0005$ .

*A priori* analysis of just amygdala voxels revealed a region of the right amygdala for which increased sustained activity was associated with improved treatment response above and beyond

initial severity (Figure 1B),  $R^2=.3$ ,  $F(1,12)=5.24$ ,  $p=.04$  and unrelated to initial severity,  $R^2<.001$ ,  $p=.98$ . Amygdala activity marginally predicted recovery status,  $X^2(1)=2.8$ ,  $p=.10$ .

### **Pre-treatment group differences in the predictive regions**

A median-split divided participants with low and high residual BDI scores. Low scorers were effectively asymptomatic after treatment,  $BDI_{final}<7$ .

*A priori* contrasts revealed that responders had marginally decreased sustained BA25 reactivity to negative words compared to non-responders (Figure 1C); 9.00 to 10.50s:  $t(12)=2.03$ ,  $p=0.06$ ,  $d=1.10$ . Exploratory group x scan x valence mixed-model analysis suggested that group differences were apparent for all valences, group x scan  $F(14,423.3)=1.78$ ,  $p=.04$  and not qualified by valence.

*A priori* contrasts revealed that depressed individuals displayed increased and sustained amygdala activity to negative words compared to controls (Figure 1D); 3.00 to 10.50s:  $t(33)=3.42$ ,  $p<0.005$ ,  $D=0.18$ ,  $d=1.18$ . Exploratory analysis confirmed group differences, group x scan  $F(14,456.3)=2.0$ ,  $p=.016$ . Exaggerated responses were present for negative words  $t(25)=3.3$ ,  $p=.003$ , but not positive or neutral words in responders; follow-up tests were not significant for non-responders, group x valence  $F(4, 704)=6.65$ ,  $p<.0005$ .

Effects were not diminished with age as a covariate.

### **Discussion**

Stronger recovery in CBT was associated with decreased subgenual cingulate (BA25) activity and increased amygdala activity to negative words before treatment. Both amygdala and BA25 display abnormal activity in depression (3-5) and their activity normalizes upon treatment, particularly with antidepressants (5, 7, 8). BA25 has been implicated in regulating limbic activity (9). Sustained amygdala activity occurred for all depressed individuals, consistent with increased

emotional reactivity. Decreased BA25 activity was specific to CBT responders suggesting deficient regulation. These data could suggest that CBT is most useful to those who demonstrate increased emotional reactivity and who cannot engage regulatory structures. Potentially CBT helps these individuals regain emotional control. Those who have neither sustained amygdala reactivity nor disrupted emotion regulation (especially BA25 function) may not benefit as much from CBT.

Sustained amygdala and BA25 reactivity to emotional stimuli were hypothesized to reflect an elaborative or ruminative coping style. Indeed, though patients' percent-change in sustained amygdala activity was not related to initial severity it was correlated with a self-report rumination scale that assesses a tendency to think repetitively about one's symptoms of depression (10);  $r=.58$ ,  $p=.03$  ( $r=.51$ ,  $p=.003$  for the depressed and controls together;  $n=32$ ). This relationship was also present in our previous sample (3). Rumination was also related to percent change in sustained BA25 activity in the depressed participants,  $r=.54$ ,  $p=.04$ , but not to residual symptomatology,  $r=-.24$ ,  $p=.4$ . Potentially, then, sustained amygdala and BA25 reactivity reflect clinically relevant substrates of rumination.

The small sample and use of a strongly hypothesis-guided task and analysis path could limit the generalizability of these results and may underestimate the potential predictive strength of imaging emotional information processing, defined more broadly. Upon larger replications, imaging of emotional information processing could aid in recommending CBT to individuals for whom it appears most appropriate, or for recommending other interventions to individuals for whom benefit is less strongly predicted.

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**Author Note**

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Figure 1: A. Region of the whole brain for which sustained BOLD signal change 6-10s following negative words presentation covaried significantly ( $p < .005$  uncorrected,  $p < .05$  corrected, 23 voxels contiguity) with residual (i.e., change in) depressive severity following Cognitive Behavior Therapy (CBT). Lower unstandardized residual post-CBT BDI scores represent better responses to CBT. Decreased BA25 activity was associated with improved response. B. Region of amygdala for which sustained BOLD signal to negative words covaried significantly ( $p < .05$ , 2 voxels contiguity small volume correction) with residual severity. Increased amygdala activity was associated with improved response. C. Empirically detected BA25 region reactivity to negative words was decreased relative to controls only for those who responded to CT. Regions of significant differences between high and low-residual BDI participants are shaded. D. Empirically detected amygdala region reactivity to negative words was increased relative to controls for all depressed individuals. Regions of significant differences between depressed and control participants are shaded.

