Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix

Methods

**Fear Conditioning Task.** The experimental protocol used in this study has been described previously(1-3). Briefly, on day 1, subjects were habituated to all task images without shock presentations (habituation phase). Subjects then underwent conditioning, in which they were shown an image of a room (an office) containing an unlit lamp. The lamp was then “turned on” to reveal one of three colors (blue, red, or yellow; eFigure 1). In the first 16 trials, two colors (reinforced conditioned stimuli, CS+, 8 trials each) were presented for 6 seconds followed by a highly annoying but not painful finger shock at a 62.5% partial reinforcement schedule, whereas the remaining 16 trials (32 total) consisted of the third color (non-reinforced conditioned stimulus, CS-) never followed by a shock. During the inter-trial interval (12-18 seconds) a black screen was presented. No shocks were administered during any subsequent experimental phase. Shortly after conditioning, extinction training occurred. During extinction training, subjects were shown images of a second room (library) with a lamp that again “turned on” for 32 trials (eFigure 1). During this extinction training phase, only two of the three stimuli were presented: one of the previously reinforced stimuli (i.e. colors) was presented (extinguished conditioned stimulus, CS+E; 16 trials) and the second was the CS- (16 trials). On day 2, subjects underwent extinction recall, during which images of the library were presented with the light “turning on” for 32 trials. Trials consisted of the CS+E (8 trials), the non-extinguished cue (reinforced cue not presented during extinction, CS+NE; 8 trials), and the CS- (16
trials). The CS+ trials were presented in two blocks during conditioning and extinction recall.

**Psychophysiological Data Acquisition and Analysis.** Skin conductance was measured simultaneously with functional MRI (fMRI) acquisition. A Coulbourn Modular Instruments System (Allentown, PA) was used to record skin conductance levels using a Coulbourn Isolated Skin Conductance Coupler (S71-23) with a constant 0.5 V through 8 mm (sensor diameter) Ag/AgCl radiotranslucent electrodes (BioPac Systems Inc., Goleta, CA). Electrodes were filled with isotonic paste and placed on the subject’s left palm 14mm apart as determined by the adhesive collar width. An Analog-to-Digital Converter (Coulbourn Lablinc V19-16) sampled and stored data on a computer. Skin conductance responses (SCRs) to the conditioned stimuli were calculated by subtracting the mean skin conductance level during the last two seconds of the context (room) presentation from the maximal skin conductance level during the cue (light color).

To assess fear acquisition during conditioning, the mean skin conductance response (SCR) during the CS+ trials was compared with the mean SCR during trials with the conditioned stimulus that was never paired with the shock (CS-) across all conditioning trials (differential conditioning measure). To assess extinction training, the mean SCRs during the first four CS+ trials was compared to the mean SCRs during the last four CS+ trials. Recall of extinction training
was assessed in two ways. First, the mean SCRs during the first two trials of extinction recall were compared between the CS+E and CS+NE. Second, the extinction retention index (ERI) was calculated, which controls for potential between individual differences during fear conditioning (10). The ERI was calculated by first dividing the mean SCRs from the first two CS+E trials during extinction recall by the maximum SCR over the CS+E trials during conditioning. This value was multiplied by 100 to obtain the percent of fear acquired, and then the resulting value was subtracted from 100 to obtain the percent of fear extinguished.

**fMRI Data Acquisition and Analysis.** Our acquisition and analysis parameters were comparable to those previously published(4-6). During all experimental phases, fMRI was performed with a Trio 3.0 Tesla whole-body, MRI system (Siemens Medical Systems, Iselin, New Jersey) equipped for echo planar imaging (EPI) with a 12-channel head coil. Subjects were instructed to restrict movement and foam cushion inserts were used to further stabilize their head. After automated scout imaging and shimming procedures were performed, a high-resolution T1 structural scan was collected (TR = 2300 ms, TE = 2.94 ms, Flip angle = 9°) with a voxel size of 1.1x0.9x1.2 mm. Functional MRI images, sensitive to blood-oxygenation level dependent (BOLD) contrast, were acquired with a descending gradient echo T2*-weighted sequence (TR= 3000 ms, TE= 30 ms, Flip angle = 90°), collected in 45 coronal oblique slices tilted 12.5° down from
the anterior-posterior commissure line. The voxel size was 3.1×3.1×3.0 mm with no gap between slices.

Each experimental phase was modeled individually. During conditioning, regressors modeled the first presentation of all CSs, early CS+s (2-4\textsuperscript{th} presentation), late CS+s (5-8\textsuperscript{th} presentations), the first shock presentation, all other shock presentations, the omitted shock, the context and the CS- (all except first presentation). Five regressors modeled stimulus onsets during extinction training: the first 8 CS+E presentations (early CS+E; reflective of recalling the fear memory), the last 8 CS+E presentations (late CS+E; reflective of extinction learning), the first 8 CS- presentations (early CS-), the last 8 CS- presentations (late CS-) and the context. During extinction recall, separate regressors modeled the first 4 (early; reflective of extinction recall) CS+E and CS+NE, the last 4 (late, reflective of re-extinction) CS+E and CS+NE, the context, the first 4 CS- during the CS+E, the first 4 CS- during the CS+NE, and the all remaining 8 CS-presentations. The analytic approach of dividing the trials into early and late phases is based on our previous studies (1,2,3). This approach was guided by previous electrophysiological animal studies showing that amygdala responses are strongest during early conditioning for example, that early extinction resembles recall of conditioning memory, and that strongest correlates of fear extinction are mostly noted during the early phase of extinction recall(7, 8).

Signal drift and biorhythms were modeled using a high-pass temporal filter (128s) and an autoregressive AR-1 correlation model, respectively. Motion artifacts
were modeled with six motion parameters (x,y,z, roll, pitch and yaw). Activated voxels in each experimental phase were identified using a statistical model containing boxcar function representing the contrasts of interest, convolved with the SPM8 canonical hemodynamic response function. Given that each experimental phase was run and analyzed independently of the other, exclusion of data due to movement was assessed per each experimental phase, and data (i.e. number of subjects) excluded due to motion will be noted when describing the results of each experimental phase in the results section below.

**Statistical Analysis.**

Demographic and psychophysiological analyses were conducted using SPSS (version 19.0, IBM Inc). Simple bivariate regressions were used to assess relationships between ERI and Y-BOCS scores. Additional bivariate regressions were used to assess the ERI and Y-BOCS scores in relation to the percent signal change in brain regions significantly correlated with task parameters during recall. For these additional regressions, percent signal change was estimated with beta values. Beta values were extract from the peak voxels within each significant brain region, which resulted from the specific contrast, using SPM8 in conjunction with Marsbar. These beta values were imported into SPSS and added as a regression variable.

For the regression analyses conducted to correlate fear extinction and YBOCS scores with brain activations/deactivation (figures 4 and 5), we first conducted...
whole-brain regression analyses between these two variables and brain activations using the CS+E vs. CS+NE contrast during day 2. Responsivity within the dACC, cerebellum, Insular cortex, vmPFC, and PCC was found to correlate with both extinction retention index and YBOCS scores. We therefore extracted the beta weights from the functional clusters (defined based on the correlation maps, with a threshold of 0.01 and exceeding 10 voxels). These values were then entered into the step-wise regression analyses to see which of these brain regions would contribute the most to the variance in extinction retention and to YBOCS scores.

eResults

**Fear Acquisition.** Due to excessive movement (> 3 mm), MRI data from 7 subjects (3 OCD patients) were excluded from this phase conditioning, and due to insufficient skin conductance responses, 5 subjects (3 patients) were excluded from psychophysiological analyses.

**Extinction Training.** Due to excessive movement (> 3 mm), MRI data from 10 subjects (5 OCD patients) were excluded during extinction analysis. Due to insufficient skin conductance responses, 5 subjects (3 patients) were excluded from psychophysiological analyses during extinction training.

**Extinction Recall.** Due to excessive movement (> 3 mm), MRI data from 3 subjects (1 OCD patient) were excluded during recall. Due to insufficient skin conductance responses, 5 subjects (3 patients) were excluded from psychophysiological analyses during extinction recall.
conductance responses, 6 subjects (3 patients) were excluded from psychophysiological analyses during recall.
eReferences

eTable 1. Whole brain results within and between groups for conditioning, extinction and recall.

### Conditioning

**Healthy Controls: CS+ > CS-**

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<th>P FDR</th>
<th>Size</th>
<th>P FWE</th>
<th>P FDR</th>
<th>T</th>
<th>Z</th>
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### Extinction Training

**Patients (OCD): late CS+E < early CS+E**

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<th>Size</th>
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Clusters with a threshold of 10 voxels with a corrected whole brain p < 0.05 family wise error (FWE). CS+, reinforced conditioned stimulus; CS-, non-reinforced conditioned stimulus; E, extinction; OCD, obsessive-compulsive disorder.
**Table 2.** Correlations between the extracted beta values from Y-BOCS and ERI related activations during extinction recall in five brain regions: the vmPFC, cerebellum, PCC, dACC, and insula cortex.

<table>
<thead>
<tr>
<th></th>
<th>Y-BOCS</th>
<th>ERI</th>
<th>vmPFC</th>
<th>Cerebellum</th>
<th>PCC</th>
<th>dACC</th>
<th>Insula</th>
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Figure legend: Illustration of cues presented during the experiment across the different experimental phases and days.
a. Positive Correlations During Recall

b. Negative Correlations During Recall

Figure legend: Regression plots extracted from regression maps shown in figures 4 and 5 of the main text. These regressions were obtained from the five brain regions found to be correlated with Y-BOCS scores (a) and with extinction retention index during recall (b). Regressions were obtained from peak correlations within the clusters for each brain region.