

Neural basis of impaired safety signaling in Obsessive Compulsive Disorder

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The ability to assign safety to stimuli in the environment is integral to everyday functioning. A key brain region for this evaluation is the ventromedial prefrontal cortex (vmPFC). To investigate the importance of vmPFC safety signaling, we used neuroimaging of Pavlovian fear reversal, a paradigm that involves flexible updating when the contingencies for a threatening (CS+) and safe (CS-) stimulus reverse, in a prototypical disorder of inflexible behavior influenced by anxiety, Obsessive Compulsive Disorder (OCD). Skin conductance responses in OCD patients ($n = 43$) failed to differentiate during reversal compared with healthy controls ($n = 35$), although significant differentiation did occur during early conditioning and amygdala BOLD signaling was unaffected in these patients. Increased vmPFC activation (for CS+ > CS-) during early conditioning predicted the degree of generalization in OCD patients during reversal, whereas vmPFC safety signals were absent throughout learning in these patients. Regions of the salience network (dorsal anterior cingulate, insula, and thalamus) showed early learning task-related hyperconnectivity with the vmPFC in OCD, consistent with biased processing of the CS+. Our findings reveal an absence of vmPFC safety signaling in OCD, undermining flexible threat updating and explicit contingency knowledge. Although differential threat learning can occur to some extent in the absence of vmPFC safety signals, effective CS- signaling becomes crucial during conflicting threat and safety cues. These results promote further investigation of vmPFC safety signaling in other anxiety disorders, with potential implications for the development of exposure-based therapies, in which safety signaling is likely to play a key role.

Obsessive Compulsive Disorder | vmPFC | Pavlovian | fMRI | safety signals

Current behavioral therapies in anxiety-related disorders are based on Pavlovian fear extinction models. As fear extinction relies on revaluation of threatening stimuli as safe, it is critical to address how the brain processes the safety of stimuli in the environment. The ventromedial prefrontal cortex (vmPFC) is known to play a multifaceted role in integrating affective evaluative processes while mediating flexible behavior and is implicated in fear learning and anxiety-related disorders (1–7). Prefrontal inflexibility in Obsessive Compulsive Disorder (OCD) suggests rigidity in threat estimation alongside a persistent urge to perform compulsive behaviors, yet only one study has examined the neural correlates of fear learning and extinction in this disorder, implicating a maladaptive vmPFC (8).

Human fear learning studies usually involve contrasting a threatening (CS+) stimulus that is occasionally paired with a shock with a stimulus that is never paired with a shock and thus safe (CS-). When using the CS+ > CS- contrast, the vmPFC consistently exhibits negative activation values in healthy controls, indicating stronger activation to the CS- than to the CS+ in this region (1–3, 7, 9). Fear reversal (Fig. 1A), in which a once-threatening stimulus turns safe and a once-safe stimulus becomes threatening, provides the ideal model for determining the interaction between threat versus safety valuation and prefrontal flexibility, as it indicates

an especially important role for the vmPFC in the updating of the safe stimulus to provide “relief relabeling,” providing a cognitive categorization of safety to a previously threatening cue (7).

The standard behavioral therapy for OCD is exposure response prevention (ERP), which involves repeatedly exposing the patient to fear-evoking stimuli while the patient is prevented from performing any compulsions that usually provide the patient with a temporary feeling of relief (10). This type of therapy can be very challenging for patients, with many of them unable to complete or engage in ERP, which has led to the idea of modifying ERP to allow for certain safety behaviors (11). Therefore, it remains a critical question how the processing of safety could be altered in OCD.

Based on the significance of the role of the vmPFC to estimate values to guide goal-directed behavior (12) and the interference of maladaptive vmPFC functioning in a variety of tasks in OCD (5, 8, 13–17), we postulated that impaired vmPFC valuation would be central to the disorder. We sought to determine how patients with OCD perform on a task that is dependent on accurate and flexible value signaling by this prefrontal region.

We hypothesized that OCD patients would show inflexibility in updating threat and safety expectancies associated with maladaptive vmPFC safety signaling in a previously validated fear reversal paradigm (7). We compared fear reversal learning in 43 OCD patients and 35 matched healthy controls by assessing threat expectancy with skin conductance responses (SCRs) and its neural correlates with functional magnetic resonance imaging (7). Our goals were to (i) relate any differences in threat learning and reversal to group differences on the whole brain level corrected for multiple comparisons,

Significance

Assigning safety to stimuli and situations forms an important part of everyday functioning. Obsessive Compulsive Disorder (OCD) is a prototypical disorder of inflexible behavior influenced by anxiety. Here we show, using neuroimaging of fear reversal learning, which involves a previously threatening stimulus becoming safe while a previously safe stimulus becomes threatening, that OCD patients fail to differentiate a safe from a threatening stimulus only after such a reversal, as measured by skin conductance responses. This OCD impairment in safety signaling, a likely prominent component of successful exposure therapy, is predicted and mediated by altered activity in a neural salience network including the ventromedial prefrontal cortex.

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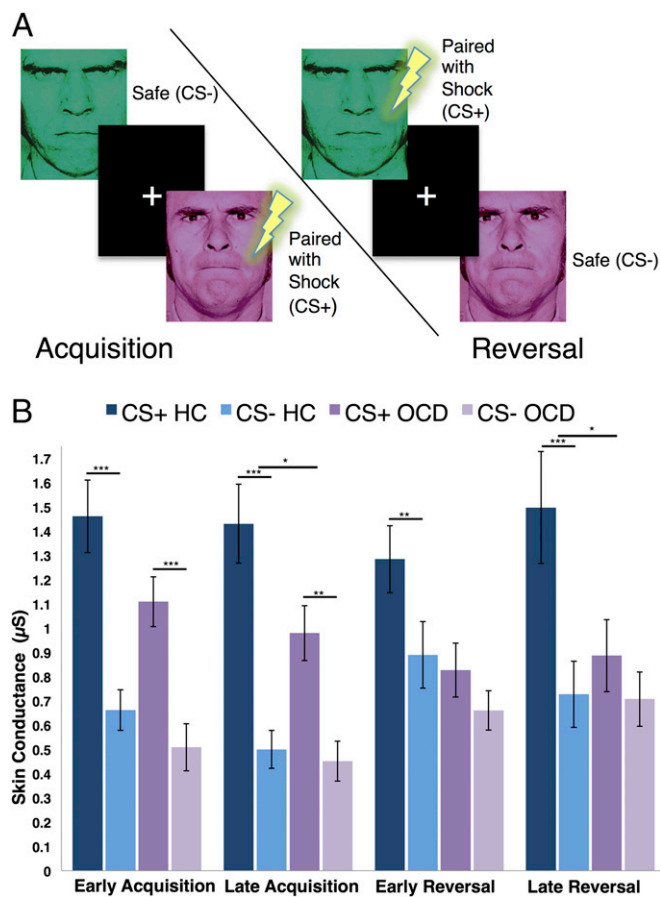


Fig. 1. Threat reversal paradigm and learning as reflected by skin conductance measurements. (A) One of the faces coterminated with a shock to the right wrist on one-third of the trials (eight CS+ US trials, which were excluded from analyses) and was therefore associated (16 CS+ trials) whereas the other face was safe (16 CS- trials), and during reversal, these contingencies were reversed so that the old CS+ became the new CS- and vice versa with the same number of trials. (B) Measured SCRs demonstrated that both OCD patients and controls acquired early ($t_{42} = 5.808, P = 0.0000007; t_{34} = 5.704, P = 0.000002$) and late ($t_{42} = 5.196, P = 0.000006; t_{34} = 6.630, P = 0.0000001$) threat learning. A between-group repeated-measures analysis with two factors (acquisition and reversal) and two stages each (early and late) revealed a significant main effect of group overall reflecting stronger differential learning in controls ($F_{1, 76} = 5.666, P = 0.02$) but also a significant Group \times Stage interaction ($F_{1, 76} = 5.87, P = 0.018$), driven by a stronger differentiation deficit in OCD patients during late acquisition ($F_{1, 76} = 5.635, P = 0.02$) and late reversal ($F_{1, 76} = 5.129, P = 0.026$) when the presence of safety signaling is required. Asterisks in figure denote level of significance (* $P < 0.05$; *** $P < 0.0001$). Images of faces used with permission from Paul Ekman, PhD/Paul Ekman, LLC.

(ii) assess the importance of the vmPFC in accurate threat reversal in OCD, and (iii) perform region of interest analyses (ROIs) for key areas in fear learning (amygdala and striatum) to investigate possible group differences. Learning was quantified as the difference between SCRs to the CS+ and CS- during acquisition and reversal, which were divided into early (first half) and late (second half) phases (Fig. 1B). The data analyses mainly used the contrast between the CS+ and CS-, which refers to the original CS+ and CS- during acquisition and the reversed CS+ and CS- during reversal.

Results

Skin Conductance Analyses Revealed Weaker Differential Learning in OCD, Driven by Significant Reductions in Differentiation During Late Acquisition and Late Reversal. To directly compare threat learning in the OCD group with controls, a between-group repeated-

measures analysis with two factors (acquisition and reversal) and two stages each (early and late) revealed a significant main effect of group overall reflecting stronger differential learning in controls ($F_{1, 76} = 5.666, P = 0.02$) but also a significant Group \times Stage interaction ($F_{1, 76} = 5.87, P = 0.018$), driven by a stronger differentiation deficit in OCD patients during late acquisition ($F_{1, 76} = 5.635, P = 0.02$) and late reversal ($F_{1, 76} = 5.129, P = 0.026$), when the presence of safety signaling is required.

Direct Comparisons Between CS+ and CS- SCRs in Each Group Show That OCD Patients Can Differentiate the CS+ Versus the CS- During Acquisition but Fail to Differentiate During Reversal. To measure contingency knowledge, we measured differential SCRs, where significantly greater responding to the CS+ compared with the CS- reflects intact contingency learning. OCD patients and healthy controls both showed highly significant early ($t_{42} = 5.808, P = 0.0000007; t_{34} = 5.812, P = 0.000002$) and late ($t_{42} = 5.196, P = 0.000006; t_{34} = 6.630, P = 0.0000001$) fear learning. However, during early and late reversal, only healthy controls differentiated the CS+ and CS- ($t_{35} = 3.274, P = 0.002; t_{35} = 3.836, P = 0.001$), whereas OCD patients failed to differentiate between stimuli during both early and late stages of reversal ($t_{42} = 1.562, P = 0.126; t_{42} = 1.056, P = 0.297$).

Our study only included OCD patients without comorbidities and was balanced in terms of males versus females compared with controls. Our study was not designed with the purpose of looking at gender differences in conditioning, but it is interesting to note that females had stronger differential conditioning than males (see *SI Materials and Methods* for statistics), irrespective of the group difference.

Whole-Brain Family Wise Error-Corrected CS+ > CS- fMRI Results. For these same learning stages, we tested for whole-brain group differences at $P < 0.05$ family wise error (FWE) corrected using a CS+ > CS- contrast. This contrast therefore always depicts the CS+ > CS- activation, which is the original CS+ > original CS- during acquisition and the updated CS+ (previous CS-) > updated CS- (original CS+) during reversal. Therefore, positive values depict stronger signaling to the CS+ and negative values depict stronger signaling to the CS-. As seen in Fig. 2A, our whole-brain results showed that the vmPFC (-3, 26, -8) contrast was significantly more positive in OCD patients compared with controls during early acquisition at the whole-brain level ($t_{76} = 7.35, P < 0.0001$ FWE, 112 voxels). Differential CS+ > CS- activity plotted for these same voxels for the following stages revealed that the vmPFC flexibly tracked the CS- in controls with below baseline activity for this contrast, whereas sustained positive contrast activity in OCD indicated persistent increased CS+ signaling for both the initial CS+ and the reversed CS+ (Fig. 2B).

These differential CS+ > CS- negative vmPFC values were significantly different from zero in controls for early acquisition ($t_{34} = -3.674, P = 0.001$), late acquisition ($t_{34} = -2.901, P = 0.006$), and late reversal ($t_{34} = -4.222, P = 0.00017$), indicating stronger vmPFC CS- signaling in controls during all stages apart from early reversal ($t_{34} = -0.126, P = 0.9$). The vmPFC in OCD patients exhibited positive vmPFC values that were significantly different from zero during all stages: early acquisition ($t_{42} = 2.381, P = 0.022$), late acquisition ($t_{42} = 2.599, P = 0.013$), early reversal ($t_{42} = 2.075, P = 0.044$), and late reversal ($t_{42} = 3.365, P = 0.002$), indicating biased responding to the CS+ in this disorder.

Additionally, our whole-brain group analyses revealed significant differences during late reversal in both the left insula (-30, 23, 1; $t_{76} = 6.55, P < 0.0001$ FWE, 260 voxels) and the left globus pallidus (-12, 2, 1; $t_{76} = 6.04, P < 0.0001$ FWE, 34 voxels), which both exhibited increased CS+ > CS- activation in controls compared with OCD patients (Fig. S1). These increased whole-brain signals in both the globus pallidus and insula for CS+ > CS- during late reversal in healthy controls further showed that

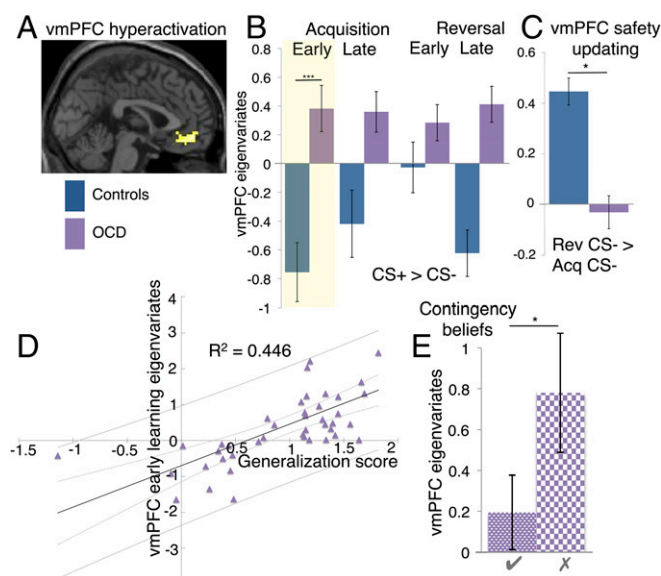


Fig. 2. vmPFC hyperactivation in OCD patients for CS+ > CS- reveals the absence of a safety signal exists from early learning and its level predicts the amount of generalization during reversal. (A) Sagittal view of the early vmPFC (-3, 26, -8) hyperactivation in OCD. (B) First eigenvariates were extracted for this vmPFC cluster ($t_{76} = 7.35$, $P < 0.0001$, FWE, 112 voxels) for all stages of learning, which showed persistence of vmPFC hyperactivation in OCD for the CS+ > CS- contrast. (C) Reversal CS- > acquisition CS- revealed a significant signal for CS- updating in controls' vmPFC (-2, 26, -2) only ($t_{76} = 5.01$, $P = 0.023$, FWE, 16 voxels). (D) vmPFC hyperactivation predicted the level of generalization in OCD patients, a score based on CS+ versus CS- differentiation during reversal at a highly significant level ($r = 0.668$, $n = 43$, $P = 0.000001$). (E) A subgroup of OCD patients (14/43) with incorrect contingency beliefs showed higher early vmPFC hyperactivation ($F_{1, 41} = 5.395$, $P = 0.025$). Asterisks in figure denote level of significance (* $P < 0.05$; *** $P < 0.0001$).

effective safety updating by the vmPFC results in a whole-brain detectable signature of accurate differential shock expectancy in brain regions preparing responses to possible threat in healthy controls but not in OCD patients (18).

Additional CS+ and CS- > Baseline fMRI Results. In addition to our main analysis investigating predictive vmPFC signaling comparing the CS+ versus the CS- to indicate relative bias of expectancies about shock expectation, we also used a mask of the voxels of the initial CS+ > CS- contrast to investigate vmPFC CS+ and CS- responding separately versus baseline [average of intertrial intervals (ITIs) when the cross was presented], as depicted in Fig. S2. These results confirmed an absence of vmPFC CS- processing in OCD (Early Acq, $t_{42} = 0.710$, $P = 0.481$; Late Acq, $t_{42} = 0.174$, $P = 0.862$; Early Rev, $t_{42} = 1.261$, $P = 0.214$; Late Rev, $t_{42} = 0.588$, $P = 0.56$) compared with mostly significant vmPFC CS+ processing (Early Acq, $t_{42} = 2.579$, $P = 0.013$; Late Acq, $t_{42} = 1.731$, $P = 0.091$; Early Rev, $t_{42} = 2.366$, $P = 0.023$; Late Rev, $t_{42} = 2.673$, $P = 0.011$). In contrast, controls sustained highly significant vmPFC CS- signaling (Early Acq, $t_{34} = 3.545$, $P = 0.001$; Late Acq, $t_{34} = 4.105$, $P = 0.000239$; Early Rev, $t_{34} = 3.696$, $P = 0.001$; Late Rev, $t_{34} = 4.034$, $P = 0.000294$) versus weak vmPFC CS+ signaling that was only marginally significant during early acquisition (Early Acq, $t_{34} = 2.055$, $P = 0.048$; Late Acq, $t_{34} = 1.73$, $P = 0.092$; Early Rev, $t_{34} = 1.144$, $P = 0.261$; Late Rev, $t_{34} = 1.251$, $P = 0.22$).

Whole-Brain FWE New CS- > Original CS- Contrast. To additionally examine updating of the safety response, we used the new CS- (both reversal stages) > original CS- (both acquisition stages) whole-brain contrast (Fig. 2C), which revealed a significantly stronger vmPFC (-2, 26, -2) signal in healthy controls compared

with the absence of such a signal in OCD patients ($t_{76} = 5.01$, $P = 0.023$, FWE, 16 voxels), indicating that updated vmPFC safety signaling is also lacking in OCD patients as expected.

vmPFC CS+ > CS- Contrast Predicts Reversal Deficit in OCD. As the vmPFC was also the only region showing whole-brain differences during early learning and is critical for safety signaling and reversal, we investigated the correlation between this difference in OCD patients and their subsequent inability to update threat estimation as reflected by their SCRs. This highly significant correlation ($r = 0.668$, $n = 43$, $P = 0.000001$) as seen in Fig. 2D showed that the OCD positive activation contrast during early fear acquisition, when learning was still intact, predicted the level of differentiation (or, inversely, generalization) between the reversed CS+ and CS-. Moreover, further examination of the correlation of early vmPFC apparent hyperactivation with CS+ and CS- SCRs for each stage revealed a significant correlation specifically with CS- SCRs during early learning ($r = 0.330$, $n = 43$, $P = 0.031$) and early reversal ($r = 0.361$, $n = 43$, $P = 0.018$), indicating a particular role for vmPFC hyperactivation in maladaptive safety responding in OCD. Furthermore, in controls, early vmPFC hypoactivation for CS+ > CS- significantly correlated with the strength of differentiation during early learning ($r = 0.462$, $n = 35$, $P = 0.005$), further supporting the notion of the important role of vmPFC safety signaling in differential threat learning. It is important to note that the common convention of using the terms “hyperactivation” and “hypoactivation” in task-related fMRI is only reflective of activation in regards to the contrast chosen. For the purposes of conventional description, we also refer to this positive CS+ > CS- contrast in OCD patients as hyperactivation.

Explicit Knowledge of the CS+ and CS- Following Reversal and Ratings of Shock Aversion. We also measured subjects' explicit knowledge of the task contingencies postexperiment. Remarkably, 14/43 OCD patients reported getting shocks to both the new CS- (old CS+) and the new CS+ (old CS-) following reversal, compared with only 2/35 of controls, corresponding to a significant difference across groups, $\chi^2(df = 1, n = 78) = 8.527$, $P = 0.0035$. In a post hoc test, we found that early vmPFC activity (Fig. 2E) was significantly higher ($F_{1, 41} = 5.395$, $P = 0.025$) in that subgroup of OCD patients with incorrect contingency knowledge ($n = 14$) compared with those OCD patients reporting the correct contingencies ($n = 29$). Participants were also asked to rate how aversive they perceived the shock to be on a scale from 1–4, and OCD patients and controls showed remarkably similar ratings (mildly aversive at averages of 2.4 and 2.5, respectively; NS, $t_{76} = -0.788$, $P = 0.433$).

Task-Related CS+ > CS- Functional Connectivity of the VmPFC. To elucidate the role of early vmPFC hyperactivation for CS+ > CS- signaling within its associated neuroanatomical circuitry, we used a psychophysiological interaction (PPI) to test for whole-brain differences between OCD patients and controls with a vmPFC ROI for the CS+ > CS- contrast for all stages (Fig. 3). OCD patients had significantly stronger task-related connectivity of the vmPFC with areas of the salience network (19) comprising the dorsal anterior cingulate (-6, 17, 31; $t_{76} = 6.81$, $P < 0.0001$, FWE, 393 voxels), left insula (-33, 20, 7; $t_{76} = 7.47$, $P < 0.0001$, FWE, 506 voxels), right insula (42, 23, 4; $t_{76} = 9.04$, $P < 0.0001$, FWE, 549 voxels), and right thalamus (12, 2, 4; $t_{76} = 6.29$, $P < 0.0001$, FWE, 56 voxels) during early acquisition only, indicating that OCD patients solely assigned salience to the CS+, whereas the CS+ and CS- were likely of similar saliency in controls.

ROIs of the Amygdala and Caudate. Previous work has established important roles for the amygdala-striatal network in aversive learning in humans (2, 20, 21), including for this paradigm (7). Hence we used ROIs (according to the original threat reversal

effective revaluation of stimuli and situations to be considered safe. During ERP, OCD patients are repeatedly confronted with tailored stimuli that normally trigger the urge to perform a compulsion and are instructed to refrain from performing their safety behavior (34). To make this therapy successful, a safety memory has to become established; otherwise, a stressful situation might trigger the return of the urge to perform such irrational yet compulsive safety behavior. The urge to perform an experimentally trained habit has been shown to be associated with hyperactivity in the caudate in OCD patients (33), whereas the vmPFC is thought to influence the caudate for goal selection (35, 36). Therefore, an aberrant vmPFC valuation system as demonstrated across several tasks in OCD (5, 17, 37) is of critical relevance to the maintenance of the disorder.

The differentiation failure during threat reversal in OCD patients was also reflected in their nondiscriminative striatal responses during this stage, likely due to the absence of the vmPFC safety signal (7). Although anxiety is often considered central to OCD, suggesting a putative role for the amygdala (38), OCD patients and controls exhibited strikingly similar amygdala processing during acquisition and reversal learning, indicating that generalization was not due to amygdala impairment and that learning of the CS+ to US association was intact in OCD. Moreover, SCRs were overall lower in OCD, likely due to the absence of the sharpening of the CS+ versus CS− contrast through safety learning, ruling out generalized anxiety related to receiving shocks, additionally confirmed by very similar shock aversion ratings as controls. These results further query the precise relationship of anxiety symptoms to obsessions and compulsions as acknowledged by the new designation of OCD without the Anxiety Disorders categorization in DSM5 and within its own category of OCDs (39). Although fear generalization may play an important role in generalized anxiety disorder (40), fear generalization in OCD only manifested itself during reversal when successful updating became contingent on an instructive vmPFC safety signal. Not only did OCD patients fail to differentiate between the threatening and updated safe stimulus during reversal, a third of them believed that they were receiving shocks to both faces, further underscoring the importance of safety valuation. Only one study to date has investigated neural correlates of fear learning and extinction in OCD (8), finding enhanced retention of fear after extinction. Our threat reversal paradigm highlights instead detrimental effects of the absence of safety signaling by the vmPFC in OCD that normally enables flexible responding to changing threats. In light of a recent study revealing that many fMRI results could reflect false positives (41), it is important to emphasize that our main findings were based on whole-brain group comparisons FEW-corrected at a significance level of $P < 0.0001$, indicative of convincing differences in vmPFC activation between OCD patients and controls. Moreover, a PET study had already implied a prominent role for the vmPFC in OCD, showing that deep brain stimulation of the

subthalamic nucleus resulted in a strong decrease in vmPFC metabolism that correlated with an improvement in Yale Brown Obsessive Compulsive (Y-BOCS) scores (30).

To summarize, our findings indicate that a maladaptive vmPFC combined with increased connectivity with areas involved in salience processing undermines accurate safety learning in OCD patients, resulting in inflexible threat beliefs. Further research into safety learning could help in the development of novel exposure-based therapies.

Materials and Methods

Participants. Forty-three OCD patients and 35 matched controls were included in our analyses. Data were collected for 46 OCD patients and 40 controls, of which we had to exclude 4 due to excessive motion artifacts (2 controls and 2 OCD patients) and 4 due to absence of skin conductance measurements (3 controls and 1 OCD patient). The majority of participants were right-handed, but we also included five left-handed participants for each group. Eligible participants reported no history of head trauma, neurological disease, substance dependence, or contraindications for MRI. Participants provided informed written consent before participation, and the Cambridge Central Research Ethics Committee approved the study. Participants' demographics are presented in Table S1 and Fig. S4. Further details about the participants are provided in SI Materials and Methods.

Threat Reversal Paradigm and Skin Conductance Measurements. In the acquisition phase, face (face A) occurred 16 times without the shock (CS+) and 8 times with the shock (CS+ US), and the other face (face B) was never paired with the shock (16 trials). In the reversal phase, these contingencies reversed, so that now face B was paired with the US on 8 trials (CS+ US), 16 times without the shock (CS−), and face A was now never paired with the US (new CS−, 16 trials). Reversal immediately and continuously followed acquisition as part of the same scanning run and was unsignaled. The order of the different trial types was pseudorandomized (no consecutive shocks and no more than two consecutive trials of any kind), and the designation of face A and face B was counterbalanced. The analyses only included the trials without a shock, meaning trials that were either a CS+, when a shock might be expected, and CS−, when a shock would never occur. SCRs were defined as the baseline to peak difference within a 7-s interval following the presentation of a CS. SCR data were normalized per participant by dividing all responses to their peak amplitude. Specifics about the paradigm, task instructions, and SCR analyses can be found in SI Materials and Methods.

Neuroimaging. All fMRI data were acquired in a single session at the Wolfson Brain Imaging Institute at Addenbrooke's Hospital using a 3 Tesla Siemens Magnetom Trio scanner. All neuroimaging acquisition, preprocessing, and analyses details (data processed in SPM8) are presented in SI Materials and Methods.

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