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Note

An initial investigation of the orbitofrontal cortex hyperactivity in obsessive-compulsive disorder: Exaggerated representations of anticipated aversive events?

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ABSTRACT

Orbitofrontal cortical (OFC) dysfunction has been repeatedly involved in obsessive-compulsive disorder, but the precise significance of this abnormality is still unclear. Current neurocognitive models propose that specific areas of the OFC contribute to behavioral regulation by representing the anticipated affective value of future events. This leads to the hypothesis that these OFC areas are hyperactive in patients, reflecting ruminative preoccupation with future aversive events. In experimental situations, such hyperactivity should be triggered by negative affect in response to high likelihood of events such as the conflict between simultaneously active incompatible responses, which can potentially lead to poor task performance. We tested this hypothesis by examining fMRI indices of brain activity of 15 OCD patients and 15 matched controls. Subjects were scanned while performing a cognitive task which involved responding to cues and subsequent probes, and some of the probes elicited response conflict. Relative to controls, the lateral OFC of patients was specifically hyperactive to cues associated with high proportion of subsequent high-conflict probes. The level of OFC hyperactivity correlated directly with the severity of anxiety symptoms. These results support the hypothesis that OCD is characterized by exaggerated OFC representations of anticipated aversive events.

1. Introduction

It has been proposed that obsessive-compulsive disorder (OCD) is associated with dysfunction in processes subserved by the fronto-striatal-thalamic-cortical loops (Rapoport, 1991; Rauch, 2000; Saxena, Brody, Schwartz, & Baxter, 1998). These pathogenetic models of the disorder emphasize the critical position of the OFC in these circuits. This cortical area has often been found hyperactive in OCD patients at rest (Alptekin et al., 2001; Kwon et al., 2003; Saxena et al., 1999, 2003, 2004; Swedo et al., 1989) and during symptom provocation (Rauch et al., 1994, 2002; Saxena et al., 1999), and this hyperactivity normalizes with successful treatment (Brody et al., 2000; Rauch et al., 2002; Saxena et al., 1999, 2003; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996; Swedo et al., 1992).

Relatively recently, the neural underpinnings of OCD have been studied using event-related functional MRI (fMRI) using cognitive tasks that depend on the integrity of fronto-striatal circuits. While the OFC is generally difficult to image using fMRI, a few recent studies detected reliable group differences in task-related OFC activity between patients and control subjects. The OFC of OCD patients has been found to be hyperactive during performance of Go-NoGo (Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005) and implicit learning of serial reaction time (SRT, Rauch et al., 2007) tasks, but hypoactive in a task requiring reversals of associations between stimuli and monetary rewards (Remijnse, Nielen, Uylings, & Veltman, 2005). Thus, the precise functional significance of these differences remains elusive.

We sought to study the nature of OFC dysfunction in OCD in the context of current theoretical frameworks from cognitive neuroscience which posit that: (1) OFC (in particular the lateral OFC) is involved in representing the anticipated negative affective value of future events (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Ursu & Carter, 2005) and (2) the simultaneous activation of multiple incompatible responses holds aversive affective value, because of its potential for inadequate performance and the increased costs of engagement of control processes necessary in order to appropriately solve this conflict (Botvinick, 2007). To this end, we performed an analysis of event-related fMRI data from a group of OCD patients and matched controls performing the AX-continous performance task (AX-CPT, Carter et al., 1998, 2000). This task involves responding to cues and subsequent probes, and some

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Table 1
Demographics and clinical measures of the patient and control groups.

Group		
Measure	Obsessive-compulsive disorder ($n = 15$)	Controls ($n = 15$)
Number of males, females	7, 8	8, 5
Age	32.06 (8.06, 22–45)	30.85 (7.96, 18–45)
Handedness (right, left)	13, 2	13, 2
Education (years)	15.8 (2.46, 12–20)	16.56 (1.93, 14–20)
YBOCS total	20.67 (5.05, 9–28)	–
YBOCS (obsessions)	10.46 (2.94, 4–14)	–
YBOCS (compulsions)	10.0 (3, 4–14)	–
STAI-S[a]	40.0[b] (9.4, 22–62)	–

Group means are reported, with standard deviation (S.D.) and range in parentheses. Demographic measures, evaluated with t tests (for mean age) and χ^2 tests (for gender composition) were not different between groups (all p values > 0.4). YBOCS: Yale-Brown Obsessive-Compulsive Scale; STAI-S: State-Trait Anxiety Inventory-State.

[a] One patient was not scored on the STAI-S inventory.

[b] Score mean was within one S.D. of normative scores for the general population, with two individual scores falling outside one S.D. of the normative scores.

of these probes elicit response conflict. A subset of these subjects had been used in a previous study (Ursu, Stenger, Shear, Jones, & Carter, 2003) examining brain activity to probes. The present analysis focused on brain responses to cues which did not elicit response conflict but instead varied with respect to their association with subsequent aversive events in the form of high-conflict probes. We tested the prediction that the lateral OFC is hyperactive in OCD patients in response to cues frequently associated with high-conflict probes, consistent with exaggerated concern for future events with negative affective value which characterize this disorder.

2. Methods

2.1. Subjects

Participants were 15 adult patients (8 females) with OCD (DSM-IV criteria) and 15 adult healthy volunteers (7 females), matched for mean age and handedness (see Supplementary material, Table 1).

Informed consent was obtained from all subjects, who were paid for participation. All procedures were approved by the Institutional Review Board of the University of Pittsburgh.

Thirteen of the 15 were medicated at the time of the study. Immediately after the scanning session, all patients were evaluated using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, Goodman et al., 1989). Fourteen of the 15 patients were also evaluated using the state version of the Spielberger State-Trait Anxiety Inventory (STAI-S, Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1980).

2.2. Behavioral task and testing procedures

Subjects were scanned while performing the AX-CPT, a modified Continuous Performance Test, described in detail in Supplementary material. Briefly, single letters were presented for 0.5 s at 12-s interval, in a continuous sequence of "cue"–"probe" pairs. Subjects were instructed to press a "target" button whenever the probe letter was an X which had been preceded by an A cue and a "non-target" button after all other stimuli (all cues and all non-X probes, henceforth referred as "Y"). For brevity, we will refer to the two types of cues as A and "B" (the latter for non-A cues), and aX, aY, bX, bY for the four types of probes (depending on what kind of cues were preceded by, see Fig. 1). The A–X sequences were frequent (70% of all cue–probe pairs), and 87.5% of the A cues were followed by an aX probe (i.e. target). This resulted in probes carrying a strong response prepotency for pressing "target", in particular X probes, and an expectation to prepare a target response after each A cue. When responding to bX and aY probes, the conflict between the prepotent target response and the correct one (non-target) had to be overcome in order to avoid errors. Thus, cues could be divided into two types critical to the hypothesis tested here: (1) a total of 48 A cues which were rarely followed by high-conflict probes (aY, 12.5% of all probes following A cues) and (2) twelve "B" cues were more often followed by high-conflict probes (bX, 50% of all probes following B cues). Thus, the "B" cues required the same response (i.e. non-target) as A cues, but the higher proportion of following high-conflict probes made them predictors of higher "potential" for negative outcomes (i.e. errors).

2.3. fMRI data acquisition and analysis

Images were acquired with a 1.5T GE Signa scanner (for detailed parameters and statistical analysis, see Supplementary material).

Brain activity during the 12 s between cues and subsequent probes was sampled by four stimulus-locked scans. Event-related analyses of the blood-oxygenation-level dependent (BOLD) responses after cues used a voxel-wise mixed ANOVA model: subject as random factor, Group (patients vs. controls) as between-group factor, Scan (1–4) and Cue type (A vs. "B") as repeated measures factors, and MR signal as dependent variable (Carter et al., 1998; MacDonald, Cohen, Stenger, & Carter, 2000; Ursu et al., 2003). Statistical maps were corrected for type I error ($p < 0.01$ in clusters of minimum four contiguous voxels in each slice, Forman et al., 1995), resulting in a volume-wise correction of $p < 0.05$. Directionality of effects was confirmed in the peak voxel by conducting t tests of the maximum signal change.

3. Results

3.1. Behavioral results

The behavioral performance of the two groups, presented in detail in Supplementary material, was contrasted by conducting random effects ANOVAs of mean reaction times (RT) and accuracy rates. In summary, the groups were matched for performance to both cues and probes, except for an overall slowing of responses in OCD patients. Two aspects of performance to probes were particularly important to our hypothesis test: (1) the bX and aY probes induce high levels of conflict, evidenced in controls by significantly increased error rates and RTs relative to aX and bY probes and (2) while nominal changes were present in the patients' error rates to probes, their accuracy was not statistically different from that of controls.

These results confirmed that B cues were followed by frequent difficult, high-conflict probes (50% bX probes), while A cues were rarely (12.5%) followed by such probes (aY probes).

3.2. Imaging results

In an exploratory Group (patients vs. controls) by Cue (A vs. "B") by Scan (S1–S4) ANOVA of the fMRI data, of the two main effects of interest (Group and Cue), only the main effect of Cue revealed two areas of activation: the left middle frontal gyrus (BA 8) and the right middle frontal gyrus (BA 9/8), both with higher activity to B cues relative to A cues.

This analysis also revealed a region with significant 3-way interaction in the right lateral OFC (see Fig. 1). The signal change in this region suggested hyperactivity in patients relative to controls in the form of sustained activity following "B" cues, but not following A cues. ANOVA of the peak signal change revealed a significant Group × Cue interaction ($F(1,28) = 6.39$, $p < 0.02$). Planned contrasts of the difference in signal change between the "B" cues and A cues confirmed that this result was due to increased "B"-related activity in the patient group ($t(14) = 2.69$, $p = 0.02$).