Published in final edited form as:

Neuropsychologia. 2009 August ; 47(10): 2145–2148. doi:10.1016/j.neuropsychologia.2009.03.018.

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

Stefan Ursu¹ and Cameron S. Carter^{1,2}

¹ Department of Psychiatry and Behavioral Sciences, University of California-Davis

² Department of Psychology, University of California-Davis

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 fifteen OCD patients and fifteen 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.

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; S. 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; S. Saxena et al., 2003; S. Saxena et al., 1999; Sanjaya Saxena et al., 2004; Swedo et al., 1989) and during symptom provocation (Rauch et al., 1994; Rauch et al., 2002; S. Saxena et al., 1999), and this hyperactivity normalizes with successful treatment (Brody et al., 2000; Rauch et al., 2002; S. Saxena et al., 2003; S. Saxena et al., 1999; Schwartz, Stoessel, Baxter, Martin, & Phelps, 1996; Swedo et al., 1992).

Corresponding author: Stefan Ursu, M.D., Ph.D., UC Davis Imaging Research Center, 4701 X St., Sacramento, CA 95817, Tel: (916) 734 4149, Fax: (916) 734 8750, E-mail: stefan.ursu@ucdmc.ucdavis.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 T, & 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) that 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-continuous performance task (AX-CPT, (Carter et al., 1998; Carter et al., 2000). This task involves responding to cues and subsequent probes, and some 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.

METHODS

Subjects

Participants were fifteen 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).

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.). 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).

Behavioral task and testing procedures

Subjects were scanned while performing the AX-CPT, a modified Continuous Performance Test, described in detail in the Supplementary material. Briefly, single letters were presented for 0.5 seconds at 12 second intervals, 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 Figure 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); 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).

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 seconds between cues and subsequent probes was sampled by 4 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 through 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 4 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.

RESULTS

Behavioral results

The behavioral performance of the two groups, presented in detail in the 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. 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).

Imaging results

In an exploratory Group (patients vs. controls) by Cue (A vs. “B”) by Scan (S1 through 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 Figure 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 $\times$ 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 ($t(14) = 2.69, p = 0.02$).

We also examined the correlations (Spearman’s r) between the peak signal changes elicited in patients by “B” cues and the individual symptoms scores in 14 patients with both STAI-S and YBOCS scores, and found that only the anxiety scores correlated significantly with “B” cue activity ($r = 0.613, p = 0.02$ and $r = 0.215, p = 0.3$, respectively). Other significant Group by Cue by Scan interactions were present in the left lateral PFC (BA 8/9), and bilateral superior temporal gyrus. In the lateral PFC these effects were due to a pattern of activity similar to that in the OFC, while in the superior temporal gyrus this statistical interaction reflected higher activity after B cues in controls relative to patients.

DISCUSSION

Our results support the hypothesis that OCD is characterized by exaggerated OFC representations of future aversive events. In our task, this manifested as increased activity to cues (the “B” cues) followed frequently by probes with negative affective value, i.e. the high conflict probes. While behavioral performance of patients was not significantly different from that of controls, the trends noted were suggestive of speed-accuracy trade-offs aimed at avoiding the possible negative effects of response conflict on accuracy of responding. Taken together, these results are consistent with the phenomenology of OCD, in which a central element is exaggerated concern with potential future negative consequences of actions.

These results point out that OFC hyperactivity in OCD is manifested independently of OCD-specific stimuli. Furthermore, the correlation with anxiety symptoms is consistent with evidence that other indices of OFC hyperactivity in OCD patients are related to the severity of anxiety (Swedo et al., 1992; Swedo et al., 1989), and with reports of OFC hyperactivity in other anxiety disorders (e.g. simple phobia, PTSD, see Rauch, Savage, Alpert, Fischman, & Jenike, 1997). Therefore, future studies should further characterize the OFC hyperactivity in OCD and compare it with other anxiety disorders in order to test its specificity to OCD as opposed to a general role in anxiety.

A recent study of reversals of associations between stimuli and monetary rewards (Remijnse et al., 2006) reported hypoactivity in OCD patients in an area of the OFC located medial and posterior to that found in our study. These differences in results could be related to the medication status of patients or the characteristics of the experimental design. It is unlikely that medication can account for these conflicting results, since several studies reporting OFC hyperactivation included either a high proportion of (Maltby et al., 2005) or exclusively (Rauch et al., 2007) medication-free patients. A second possibility is that differences in activity reflect a functional specialization of OFC subregions for processes specific to reversal tasks, such as the affective switches. A third possibility, with implications for studies comparing OCD patients and controls has to do with the choice of comparison condition. For instance, when conditions of interest were compared to frequent comparison trials carrying minimal decision making load, studies consistently reported OFC hyperactivity in patients (Maltby et al., 2005; Rauch et al., 2007; Ursu et al., 2003). In contrast, when the comparison trials were rare and required more elaborated choices such as rapid identification of relatively complex objects (Remijnse et al., 2006), the differences from the “target” condition were small and translated in generalized relative hypoactivity in patients. Thus, it is possible that given the pathological self doubt that characterizes OCD, this relative hypoactivity may in fact be driven by hypersensitivity to potential negative outcomes in the comparison trials, if they can be perceived as having significant potential for error either because they are rare (and thus less

familiar), or because of the intrinsic uncertainty of their decision making requirements (Critchley, Mathias, & Dolan, 2001). Uncertainty regarding the upcoming probe could also be an alternative account for the increased “B” cue activity reported here. However, it is likely that this explanation is not fundamentally different from our hypothesis, since the probes following “B” cues carried high outcome uncertainty (i.e. 50% were probes with potential for conflict-induced errors) but not response uncertainty (i.e. the correct response was always “non-target”).

These preliminary results emphasize the need for replication in future studies of OCD. In order to precisely characterize the link between exaggerated concern for potential negative outcomes and the OFC dysfunction in OCD, such studies should include more direct manipulations of anticipated outcomes of actions, direct contrasts between activity in the OFC and that in other cortical areas (e.g. the insula) thought to play a role in trait anxiety (Simmons, Strigo, Matthews, Paulus, & Stein, 2006; Stein, Simmons, Feinstein, & Paulus, 2007), as well as explicit manipulations of the experimental conditions used as reference.

References

- Alptekin K, Degirmenci B, Kivircik B, Durak H, Yemez B, Derebek E, et al. Tc-99m HMPAO brain perfusion SPECT in drug-free obsessive-compulsive patients without depression. *Psychiatry Res* 2001;107(1):51–56. [PubMed: 11472864]
- Botvinick MM. Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn Affect Behav Neurosci* 2007;7(4):356–366. [PubMed: 18189009]
- Brody AL, Saxena S, Fairbanks LA, Alborzian S, Demaree HA, Maidment KM, et al. Personality changes in adult subjects with major depressive disorder or obsessive-compulsive disorder treated with paroxetine. *Journal of Clinical Psychiatry* 2000;61(5):349–355. [PubMed: 10847309]
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 1998;280(5364):747–749. [PubMed: 9563953]
- Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, et al. Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences of the United States of America* 2000;97(4):1944–1948. [PubMed: 10677559]
- Critchley HD, Mathias CJ, Dolan RJ. Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron* 2001;29(2):537–545. [PubMed: 11239442]
- Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonance in Medicine* 1995;33(5):636–647. [PubMed: 7596267]
- Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry* 1989;46(11):1006–1011. [PubMed: 2684084]
- Kwon JS, Kim JJ, Lee DW, Lee JS, Lee DS, Kim MS, et al. Neural correlates of clinical symptoms and cognitive dysfunctions in obsessive-compulsive disorder. *Psychiatry Res* 2003;122(1):37–47. [PubMed: 12589881]
- MacDonald AW 3rd, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 2000;288(5472):1835–1838. [PubMed: 10846167]
- Maltby N, Tolin DF, Worhunsky P, O’Keefe T M, Kiehl KA. Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. *Neuroimage* 2005;24(2):495–503. [PubMed: 15627591]
- O’Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci* 2001;4(1):95–102. [PubMed: 11135651]

- Rapoport JL. Recent advances in obsessive-compulsive disorder [see comments]. *Neuropsychopharmacology* 1991;5(1):1–10. [PubMed: 1930606]
- Rauch SL. Neuroimaging research and the neurobiology of obsessive-compulsive disorder: where do we go from here? *Biol Psychiatry* 2000;47(3):168–170. [PubMed: 10682213]
- Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, Savage CR, et al. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography [see comments]. *Archives of General Psychiatry* 1994;51(1):62–70. [PubMed: 8279930]
- Rauch SL, Savage CR, Alpert NM, Fischman AJ, Jenike MA. The functional neuroanatomy of anxiety: a study of three disorders using positron emission tomography and symptom provocation. *Biological Psychiatry* 1997;42(6):446–452. [PubMed: 9285080]
- Rauch SL, Shin LM, Dougherty DD, Alpert NM, Fischman AJ, Jenike MA. Predictors of Fluvoxamine Response in Contamination-related Obsessive Compulsive Disorder. A PET Symptom Provocation Study. *Neuropsychopharmacology* 2002;27(5):782–791. [PubMed: 12431852]
- Rauch SL, Wedig MM, Wright CI, Martis B, McMullin KG, Shin LM, et al. Functional magnetic resonance imaging study of regional brain activation during implicit sequence learning in obsessive-compulsive disorder. *Biol Psychiatry* 2007;61(3):330–336. [PubMed: 16497278]
- Remijnse PL, Nielen MM, Uylings HB, Veltman DJ. Neural correlates of a reversal learning task with an affectively neutral baseline: An event-related fMRI study. *Neuroimage* 2005;26(2):609–618. [PubMed: 15907318]
- Remijnse PL, Nielen MM, van Balkom AJ, Cath DC, van Oppen P, Uylings HB, et al. Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. *Arch Gen Psychiatry* 2006;63(11):1225–1236. [PubMed: 17088503]
- Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr. Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *Am J Psychiatry* 2003;160(3):522–532. [PubMed: 12611834]
- Saxena S, Brody AL, Maidment KM, Dunkin JJ, Colgan M, Alborzian S, et al. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. *Neuropsychopharmacology* 1999;21(6):683–693. [PubMed: 10633474]
- Saxena S, Brody AL, Maidment KM, Smith EC, Zohrabi N, Katz E, et al. Cerebral Glucose Metabolism in Obsessive-Compulsive Hoarding. *Am J Psychiatry* 2004;161(6):1038–1048. [PubMed: 15169692]
- Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *British Journal of Psychiatry -Supplement* 1998;35:26–37. [PubMed: 9829024]
- Schwartz JM, Stoessel PW, Baxter LR Jr, Martin KM, Phelps ME. Systematic changes in cerebral glucose metabolic rate after successful behavior modification treatment of obsessive-compulsive disorder. *Archives of General Psychiatry* 1996;53(2):109–113. [PubMed: 8629886]
- Simmons A, Strigo I, Matthews SC, Paulus MP, Stein MB. Anticipation of aversive visual stimuli is associated with increased insula activation in anxiety-prone subjects. *Biol Psychiatry* 2006;60(4):402–409. [PubMed: 16919527]
- Spielberger, CD.; Gorsuch, RL.; Lushene, R.; Vagg, PR.; Jacobs, GA. *Manual for the state-trait anxiety inventory*. Palo Alto: Consulting Psychology Press; 1980.
- Stein MB, Simmons AN, Feinstein JS, Paulus MP. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *Am J Psychiatry* 2007;164(2):318–327. [PubMed: 17267796]
- Swedo SE, Pietrini P, Leonard HL, Schapiro MB, Rettew DC, Goldberger EL, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. *Archives of General Psychiatry* 1992;49(9):690–694. [PubMed: 1514873]
- Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A, et al. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Archives of General Psychiatry* 1989;46(6):518–523. [PubMed: 2786402]
- Ursu S, Carter CS. Outcome representations, counterfactual comparisons and the human orbitofrontal cortex: implications for neuroimaging studies of decision-making. *Brain Res Cogn Brain Res* 2005;23(1):51–60. [PubMed: 15795133]

Ursu S, Stenger VA, Shear MK, Jones MR, Carter CS. Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. *Psychol Sci* 2003;14(4):347–353. [PubMed: 12807408]

Figure 1.

a) Example sequence of 10 stimuli used in the experiment. The first 4 stimuli represent AX cue-probe pairs, followed by A-“Y”, “B”-X and “B”-“Y” pairs. On the scan timeline, each mark symbolizes a 3 second functional scan. In it, shaded areas highlight the scans included in the current event-related analysis: blue epochs mark the A cue activity, red epochs mark “B” cue activity. b) Statistical map of F values of the Group $\times$ Cue $\times$ Scan ANOVA of the MR signal. The lateral orbitofrontal region with significant Group by Cue by Scan interaction included 27 voxels with the peak at Talairach coordinates 36, 32, -10. The interaction reflects increased activity to “B” cues relative to A cues in the patient group, versus no difference between the two cue types in controls, consistent with increased sensitivity of patients’ OFC to stimuli associated with potential for subsequent negative outcomes (i.e. high response conflict probes). The color bar represents range of F values.

Table 1

Demographics and clinical measures of the patient and control groups.

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 (SD) 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 SD of normative scores for the general population, with 2 individual scores falling outside one SD of the normative scores.