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Aberrant error processing in relation to symptom severity in obsessive–compulsive disorder: A multimodal neuroimaging study

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ABSTRACT

Background: Obsessive–compulsive disorder (OCD) is characterized by maladaptive repetitive behaviors that persist despite feedback. Using multimodal neuroimaging, we tested the hypothesis that this behavioral rigidity reflects impaired use of behavioral outcomes (here, errors) to adaptively adjust responses. We measured both neural responses to errors and adjustments in the subsequent trial to determine whether abnormalities correlate with symptom severity. Since error processing depends on communication between the anterior and the posterior cingulate cortex, we also examined the integrity of the cingulum bundle with diffusion tensor imaging.
Methods: Participants performed the same antisaccade task during functional MRI and electroencephalography sessions. We measured error-related activation of the anterior cingulate cortex (ACC) and the error-related negativity (ERN). We also examined post-error adjustments, indexed by changes in activation of the default network in trials surrounding errors.
Results: OCD patients showed intact error-related ACC activation and ERN, but abnormal adjustments in the post- vs. pre-error trial. Relative to controls, who responded to errors by deactivating the default network, OCD patients showed *increased* default network activation including in the rostral ACC (rACC). Greater rACC activation in the post-error trial correlated with more severe compulsions. Patients also showed increased fractional anisotropy (FA) in the white matter underlying rACC.
Conclusions: Impaired use of behavioral outcomes to adaptively adjust neural responses may contribute to symptoms in OCD. The rACC locus of abnormal adjustment and relations with symptoms suggests difficulty suppressing emotional responses to aversive, unexpected events (e.g., errors). Increased structural connectivity of this paralimbic default network region may contribute to this impairment.

1. Introduction

Obsessive–compulsive disorder (OCD) is characterized by stereotyped and repetitive behaviors that persist despite feedback. These behaviors serve to reduce distress, but are often excessive and not realistically connected to the feared outcome they are intended to prevent. For example, an individual with OCD may feel compelled to repeatedly check that the door is locked despite having just locked the door, 'knowing' that the door is locked, and wanting to stop. In this scenario, the distressing feeling that the door is not locked persists despite clear evidence to the contrary and compels repetitive checking. Such repetitive, maladaptive behaviors may reflect impaired use of feedback about outcomes (e.g., a locked door) to adjust emotional (e.g., distress) and behavioral (e.g., checking) responses. Here, we used multimodal neuroimaging to test the hypothesis that impaired use of outcomes – in this study, errors – to adaptively adjust future responses characterizes OCD and contributes to symptoms. Since error processing involves (*i*) recognizing that an error has occurred and (*ii*) adjusting future responses and since deficits in either of these abilities could contribute to rigid, repetitive behavior, we examined the neural and behavioral markers of each.

We used an antisaccade paradigm to study error processing. Antisaccades require inhibition of the prepotent response of looking towards a suddenly appearing stimulus and the substitution of a gaze in the opposite direction. Antisaccade errors (i.e., looking towards the stimulus) reliably elicit neural and behavioral error markers (Agam et al., 2011; Belopolsky and Kramer, 2006; Endrass et al., 2007; Klein et al., 2007; Nieuwenhuis et al., 2001; Polli et al., 2005). We first investigated whether individuals with OCD show intact error detection as indexed by error self-correction and two extensively characterized and highly reliable neural error markers: the error-related negativity (ERN) as measured by electroencephalography (EEG) and functional

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MRI (fMRI) activation of the anterior cingulate cortex (ACC). These error markers have been theorized to index error-based reinforcement learning (Holroyd and Coles, 2002), mismatch or conflict monitoring (Carter and van Veen, 2007; Falkenstein et al., 2000; Yeung et al., 2004), increased cognitive control (Kerns et al., 2004) and the emotional response to errors (Proudfit et al., 2013). Prior studies of OCD have demonstrated an exaggerated ERN (Carrasco et al., 2013; Endrass et al., 2008, 2010; Gehring et al., 2000; Johannes et al., 2001; but see Nieuwenhuis et al., 2005; Ruchsow et al., 2005; Xiao et al., 2011), increased rostral ACC (rACC) and/or dorsal ACC (dACC) activation following errors (Fitzgerald et al., 2005, 2010; Maltby et al., 2005; Stern et al., 2011; Ursu et al., 2003), and inappropriate error signaling on correct trials in some (Maltby et al., 2005; Ursu et al., 2003), but not all studies (Fitzgerald et al., 2005; Gehring et al., 2000). We expected to replicate prior findings that exaggerated error signaling correlates with symptom severity in OCD (Fitzgerald et al., 2005; Gehring et al., 2000; Ursu et al., 2003). This would support the theory that inappropriate and exaggerated error signaling leads to a pervasive sense of incompleteness and self-doubt and triggers compulsions to repeat behaviors (Maltby et al., 2005; Pitman, 1987).

Second, we investigated whether patients with OCD use errors to adjust future responses. To this end we examined post-error slowing (PES; Rabbitt, 1966), or the slowing of responses in trials that follow errors, and its neural correlates. Over trials, responses speed up until an error is committed (i.e., pre-error speeding; Gehring and Fencsik, 2001; Ridderinkhof et al., 2003) and following errors, responses slow down, presumably to reduce the probability of another error. (PES does not always lead to better performance, however, alternative accounts of its function exist (for review see, Danielmeier and Ullsperger, 2011) including that it reflects an orienting response to infrequent events (Notebaert et al., 2009).) These adjustments of reaction time (RT) are paralleled by changes in activity of the brain's default network (Agam et al., 2013). The default network, which is thought to mediate self-referential and affective processing, is typically deactivated during effortful cognitive performance, presumably reflecting reduced focus on the internal milieu (Buckner et al., 2008). During trials immediately preceding errors (Agam et al., 2013; Eichele et al., 2008; Li et al., 2007) and during error trials (Agam et al., 2013; Polli et al., 2005), there is a relative failure of this task-induced deactivation, suggesting that interference from internally directed thought culminates in an error. In trials that follow errors, task-induced deactivation is re-instated (Eichele et al., 2008), suggesting a shift in focus from the internal milieu back to the task-at-hand (Agam et al., 2013). Such dynamic modulations of attention and performance in response to outcomes are fundamental to adaptive, flexible behavior and we hypothesized that individuals with OCD would show abnormal post-error adjustments. We compared RT in correct trials immediately preceding an error and correct trials immediately following an error (i.e., PES), and the corresponding pattern of default network activation, as we have done in our prior work (Agam et al., 2011, 2013). Use of only pre-error and post-error correct trials maximizes sensitivity to changes in performance and activation based on error history because it minimizes contamination by global fluctuations in performance over time that affect comparisons that include all correct trials that follow a correct response (Dutilh et al., 2012). We expected that abnormal adjustments in the trial after an error in OCD would correlate with symptom severity.

We also examined error positivity or Pe (van Veen and Carter, 2002), an event-related potential occurring approximately 300–500 ms following an error (for review see, Overbeek et al., 2005). The Pe is less consistently observed than the ERN and is thought to index error awareness (Endrass et al., 2007; Nieuwenhuis et al., 2001; Wessel et al., 2011) and/or the subjective appraisal of errors (van Veen and Carter, 2002) and has been associated with PES (Nieuwenhuis et al., 2001).

Finally, we examined the microstructural integrity of the cingulum bundle using diffusion tensor imaging (DTI) measures of fractional anisotropy (FA). The cingulum bundle contains direct white matter connections between the ACC and the posterior cingulate cortex (PCC) (Schmahmann et al., 2007), and recent evidence suggests that these regions work together to mediate error processing (Agam et al., 2011). The rACC and PCC are also key anatomical components of the default network, whose activation corresponds with PES (Agam et al., 2013) and may mediate post-error adjustments. We investigated whether abnormal cingulate cortex function in OCD is accompanied by abnormal structural connectivity.

In summary, we expected OCD to be characterized by exaggerated and inappropriate error signaling and aberrant neural and behavioral adjustments following errors. Further, we expected that these abnormalities would predict symptom severity and have an anatomic correlate in the microstructural integrity of the cingulum bundle.

2. Methods

2.1. Participants

Sixty patients from the Obsessive–Compulsive and Related Disorders Program at Massachusetts General Hospital were enrolled. Twenty-seven met the following inclusion criteria and were referred for scanning: OCD based on a Structured Clinical Interview for DSM-IV (First et al., 1997); Yale–Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989a,b) total score >16; no co-morbid Axis I disorder with the exception of anxiety disorders and depression; and unmedicated or on stable medications for at least 8 weeks. Twenty-one of the 27 OCD patients referred for scanning completed the study. These participants had Y-BOCS scores of 11 ± 3 (mean ± SD) obsessions, 12 ± 3 compulsions, and 23 ± 5 total. Table S1 provides co-morbidity and medications.

Twenty healthy control participants, screened to exclude a personal history of mental illness (SCID — Non-patient Edition; First et al., 2002) and a family history of anxiety disorder, were recruited from the community by poster and website advertisements.

All participants were screened to exclude substance abuse or dependence within the preceding six months and any independent condition that might affect brain function. OCD patients were characterized with the Beck Depression Inventory-II (BDI-II, Beck, 1996) and Beck Anxiety Index (BAI; Beck et al., 1988; Table S1). The final groups of 21 OCD patients and 20 controls did not differ significantly in age, sex, years of education, handedness based on the modified Edinburgh Handedness Inventory (Oldfield, 1971; White and Ashton, 1976), or estimated verbal IQ based on the Wide Range Achievement Test-III Reading portion (Wilkinson, 1993) (Table 1). The study was approved by the Partners Human Research Committee and all participants gave written informed consent.

All participants were included in DTI analyses. To obtain reliable estimates of differences in activation, only participants with a minimum of ten usable error trials (Olvet and Hajcak, 2009; Pontifex et al., 2010)

Table 1
Means, standard deviations, and group comparisons of demographic data. The Phi value is the result of a Fisher's exact test. The z value is the result of a nonparametric Mann–Whitney U comparison.

Subject characteristics	Healthy controls (n = 20)	OCD (n = 21)	t	p
Age	33 ± 11	33 ± 11	0.07	.94
Sex	11M/9F	8M/13F	ϕ = .17	.35
Years of education	17 ± 2	16 ± 1	1.33	.19
Laterality score (handedness)[a]	65 ± 55	74 ± 34	0.62	.54
Estimated verbal IQ[b]	113 ± 6	110 ± 11	1.10	.28

[a] Laterality scores of −100 and +100 denote exclusive use of left or right hand, respectively.
[b] Two control participants and one OCD patient were not administered the WRAT-III because they were non-native English speakers.