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Neural correlates of working memory deficits and associations to response inhibition in obsessive compulsive disorder

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ABSTRACT

Previous research in patients with obsessive-compulsive disorder (OCD) has indicated performance decrements in working memory (WM) and response inhibition. However, underlying neural mechanisms of WM deficits are not well understood to date, and empirical evidence for a proposed conceptual link to inhibition deficits is missing.

We investigated WM performance in a numeric n-back task with four WM load conditions during functional Magnetic Resonance Imaging (fMRI) in 51 patients with OCD and 49 healthy control participants who were matched for age, sex, and education. Additionally, a stop signal task was performed outside the MRI scanner in a subsample.

On the behavioral level, a significant WM load by group interaction was found for both accuracy ($p < 0.02$) and reaction time measures ($p < 0.03$), indicating increased reaction times as well as reduced accuracy specifically at high WM load (3-back) in patients with OCD. Whole-brain analyses of fMRI-data identified neural correlates of a load-dependent WM decrement in OCD in the supplementary motor area (SMA) and the inferior parietal lobule (IPL). Within the OCD sample, SMA-activity as well as n-back performance were correlated with stop signal task performance.

Results from behavioral and fMRI-analyses indicate a reduced WM load-dependent modulation of neural activity in OCD and suggest a common neural mechanism for inhibitory dysfunction and WM decrements in OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) affects approximately 2–3% of the population (Ruscio et al., 2010) and is associated with highly unpleasant obsessive thoughts and compulsive behaviors in the majority of patients (Mendlowicz and Stein, 2000) that strongly impair their everyday lives. Empirical evidence suggests that besides these clinical symptoms, OCD is related to cognitive dysfunctions (Abramovitch et al., 2013; Shin et al., 2014; Snyder et al., 2014) mainly in executive functions (e.g., inhibition and shifting) and complex memory tasks such as working memory (WM) updating (de Vries et al., 2014; Harkin and Kessler, 2011; Koch et al., 2012; Purcell et al., 1998; van der Wee et al., 2003). Studies on the neural underpinnings of cognitive deficits in OCD have repeatedly reported dysregulations in fronto-striatal networks (Casale et al., 2011; Pauls et al., 2014). In OCD, a reduced inhibition of projections from the striatum to the thalamus and further to prefrontal cortex is thought to play a role in imbalanced fronto-striatal circuits and was found to relate to inhibition deficits in OCD (Chamberlain et al., 2005, 2006). In the context of WM, this dysfunction could be associated with a deficient updating of information in prefrontal cortex (Chatham et al., 2011; Frank et al., 2001). At the same time, alterations in the functioning of a fronto-parietal network that is specifically relevant for WM processing, have been proposed in OCD (Melloni et al., 2012; Menzies et al., 2008). Despite relatively strong evidence for deficits in executively demanding WM tasks (e.g., WM updating), their underlying neural mechanisms are not well understood to date, and previous results have been heterogeneous showing both increased and decreased activations in fronto-parietal WM-related areas (de Vries et al., 2014; Henseler et al., 2008; Koch et al., 2012; Nakao et al., 2009; van der Wee et al., 2003). A recent

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study by Koch et al. (2012) suggested that inconsistencies could be reduced by taking differences in task demand into account, indicating that patients with OCD may show increased prefrontal activations at low task demand (low WM load) and decreased activations at high task demand (high WM load) when tested against healthy controls (HC). Such a pattern has been described in terms of a reduced WM load-dependent modulation of neural activity (Heinzel et al., 2014; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008).

Recent hypotheses explaining OCD-related alterations in brain activations and performance during WM have suggested that impaired WM in OCD may relate to difficulties in focusing on the relevant information and failures to inhibit irrelevant stimuli (de Vries et al., 2014). While such a mechanism has been demonstrated in healthy older subjects (Gazzaley et al., 2005), and appears plausible in the context of OCD, it has not been specifically investigated in OCD, to date. Key regions within a fronto-parietal network that were found to be commonly activated during both WM updating and response inhibition in healthy participants include the (pre-) supplementary area (SMA), the lateral inferior frontal gyrus (IFG), and the inferior parietal lobule (IPL); see (Nee et al., 2013) for a meta-analysis for executive components of WM and (Boehler et al., 2010) for a conjunction analysis in response inhibition. Most importantly, SMA has been reported to show aberrant activations in OCD during WM (de Vries et al., 2014) as well as inhibitory control tasks (de Wit et al., 2012; Grützmann et al., 2016).

Current investigations of OCD-related alterations in functional connectivity have proposed that dysregulations of fronto-parietal neural activations may be associated with altered limbic-frontal connectivity (de Vries et al., 2014). More specifically, the authors found an increased functional connectivity between Amygdala and SMA in low-performing patients with OCD that was interpreted in terms of an increased uncertainty of their task performance (Stern et al., 2013).

Since previous fMRI research in OCD has mainly focused on visuospatial WM tasks (de Vries et al., 2014), one aim of our study was to test if similar alterations in neural activation and connectivity can be found during a numeric n-back task as well, indicating a more general underlying dysfunction of WM deficits in OCD. It is investigated if altered frontal activity, as reported in previous visuospatial n-back studies, is also found in this numeric n-back study. This finding would support the notion of a dysfunctional involvement of content-unspecific executive components of WM (Baddeley, 2003) as a possible underlying neural mechanism of WM decrements in OCD.

Thus, for the first time, we adopted a numeric n-back paradigm with four different WM load conditions (Heinzel et al., 2014) during fMRI in a relatively large sample of OCD and HC participants, in the current study. Since a subsample also participated in a stop signal task, we were able to explore the relationship between neural activation patterns during WM performance and inhibitory performance in the stop signal task for the first time in OCD. The following hypotheses were tested:

1) Patients with OCD would show both lower accuracy and higher reaction times in an n-back task, specifically at high WM load.
2) Patients with OCD would show increased activation at low and decreased activation at high WM load in fronto-parietal WM regions, indicating reduced WM load-dependent modulation of neural activity.
3) Patients with OCD would show increased connectivity between Amygdala and frontal WM regions.
4) Analyses within the OCD group would show a negative correlation between fronto-parietal WM load-dependent modulation of neural activity and OCD symptoms.
5) Exploratory analyses in a subsample of participants that performed a stop signal task would show a
   a. positive relationship between n-back and stop signal performance in the OCD sample.
   b. positive relationship between SMA activity during n-back and stop signal performance in the OCD sample.

Table 1
Demographics of healthy control (HC) and obsessive-compulsive patient (OCD) samples. Means and standard deviations (in parentheses) are shown. Units: Age [years]; Verbal test score [sum score]; Y-BOCS [sum score]; Performance [% correct]; Reaction time [ms].

Measure	HC (N = 49)	OCD (N = 51)	p =
Age	30.92 (7.31)	33.00 (9.73)	0.231
Sex	20 m/29 f	26 m/25 f	0.324
Verbal test score	32.16 (3.72)	31.20 (4.78)	0.263
Y-BOCS severity scale (sum)[a]	n. a.	23.25 (5.21)	n. a.
Y-BOCS subdimension taboo	n. a.	3.10 (2.77)	n. a.
Y-BOCS subdimension contamination	n. a.	4.33 (3.37)	n. a.
Y-BOCS subdimension rituals	n. a.	2.41 (2.48)	n. a.
Y-BOCS subdimension hoarding	n. a.	4.47 (2.85)	n. a.
Y-BOCS subdimension doubt	n. a.	4.12 (2.85)	n. a.
Comorbid axis I disorder[b]	n. a.	43	n. a.
Current medication[c]	n. a.	22	n. a.
Performance 0-back	99.62 (1.22)	97.89 (5.07)	**0.022**
Performance 1-back	96.87 (5.79)	96.62 (5.41)	0.823
Performance 2-back	83.6 (14.58)	81.18 (15.22)	0.426
Performance 3-back	82.44 (18.75)	72.33 (23.82)	**0.021**
Reaction time 0-back	380 (45)	391 (55)	0.297
Reaction time 1-back	439 (62)	471 (86)	**0.033**
Reaction time 2-back	545 (85)	582 (93)	**0.039**
Reaction time 3-back	531 (101)	598 (119)	**0.003**

Bold p-values indicate significance at $p < 0.05$.

[a] Subdimensions of Y-BOCS according to Katerberg et al. (2010).

[b] Comorbid mental disorders: 44 mood disorders, 15 anxiety disorders, 3 eating disorders, 2 somatoform disorder, 1 tic disorder, 1 cannabis abuse. 16 OCD patients had more than one comorbid disorder.

[c] 19 SSRIs, 4 SSNRIs, 5 tricyclic antidepressants, 2 neuroleptics, 1 benzodiazepine.

2. Materials and methods

2.1. Participants

Fifty-four patients with OCD were recruited from the OCD out-patient clinic at Humboldt-University Berlin and 56 healthy control (HC) participants were recruited via online advertisements. The OCD group was interviewed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) by licensed clinical psychologists and diagnosed using the German version of the Structured Clinical Interview for DSM-IV (SCID). Four participants in the HC and two in the OCD sample had to be excluded from data analyses due to technical failures during fMRI scanning. Furthermore, three participants in the HC and one in the OCD sample showed performance at chance level (performance below 30% hitrate or above 30% false alarm rate) in the WM task, and thus, had to be excluded from data analyses as well. Therefore, the final analysis sample consisted of 51 patients with OCD and 49 HC (see Table 1 for demographic data). All participants had normal or corrected-to-normal vision, and no history of any neurological diseases or brain injuries. The study was approved by the local Ethics Committee of the Humboldt-Universität zu Berlin and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after the procedures had been fully explained. As this study was part of a larger project, a subsample of 41 patients with OCD and 29 HC also had participated in a stop-signal paradigm outside the MRI scanner. Stop signal reaction time (SSRT) could not be reliably estimated in one OCD patient (performance below 2.5 standard deviations from the mean), and therefore, this participant was excluded from analyses that included SSRT.

2.2. N-back paradigm during fMRI

A modified version of the n-back paradigm with numerical stimuli as described in the study of Heinzel et al. (2014) was used in this study. Sixteen blocks (4 blocks of each 0-, 1-, 2-, and 3-back) were presented in three different pseudo-randomized orders counterbalanced across subjects. The total duration of the task was 9 min. Please refer to the