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Association between hippocampus volume and symptom profiles in obsessive–compulsive disorder

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ABSTRACT

Background: The hippocampus has recently been identified to play a key role in the pathophysiology of adult obsessive-compulsive disorder (OCD). Surprisingly, there is only limited evidence regarding the potential relationships with symptom dimensions. Due to the heterogeneity of symptoms in OCD, we aimed at further examining, whether hippocampal volume differences might be related to symptom profiles instead of single symptom dimensions.

Methods: In order to find out more about the potential association between clinical symptom profiles and alterations in hippocampal volume we categorized a large sample of OCD patients ($N = 66$) into distinct symptom profile groups using K-means clustering. In addition, hippocampal volumes of the different symptom profile groups were compared with hippocampal volumes in a sample of 66 healthy controls.

Results: We found significant differences in hippocampal volume between the different symptom profile groups which remained significant after correcting for age, sex, total intracranial volume, OCI-total score, depression, medication, disease duration and scanner. The patient group characterized by overall lower symptom scores and without high symptom severity in any specific domain showed the highest hippocampal volume. Finally, the comparison with healthy controls demonstrated significantly lower hippocampal volumes in those patients whose symptom profile was characterized by a high severity of ordering and checking symptoms.

Conclusions: Present results provide further confirmation for alterations in hippocampus structure in OCD and suggest that symptom profiles which take into account the multi-symptomatic character of the disorder should be given greater attention in this context.

1. Introduction

Despite increasing evidence for structural brain alterations in obsessive-compulsive disorder (OCD) the overall picture has to be considered as rather heterogeneous with findings reporting both increases and decreases in gray matter volume, thickness, surface area or gyrification (Fan et al., 2013; Kuhn et al., 2013; Nakamae et al., 2012; Piras et al., 2015; Rus et al., 2016; Shaw et al., 2015; Shin et al., 2007; Venkatasubramanian et al., 2012; Wobrock et al., 2010). In an attempt to reduce overall result heterogeneity and to filter out the most meaningful alterations, an increasing number of meta-analyses pooling data from multiple OCD sites worldwide are emerging in the OCD research community (Boedhoe et al., 2017; De Wit et al., 2014; Fouche et al., 2017). The ENIGMA consortium analysis constitutes the largest meta-analysis on structural alterations in OCD to date. Employing a coordinated and standardized analysis approach, meta- and mega-analysis of data from 1830 OCD patients ($N = 335$ children, $N = 1495$ adults) and 1759 controls was conducted to identify alterations in subcortical brain volumes in OCD patients compared to healthy controls (Boedhoe et al., 2017). As one of the main findings the analysis revealed the adult patient sample to have significantly increased pallidum and significantly smaller hippocampus volumes compared to healthy controls. The pallidum is regarded as one of the core regions within the frequently discussed cortico-striato-thalamo-cortical (CSTC) circuit. A dysbalance within this circuit is assumed to represent a central psychopathological mechanism underlying obsessions and compulsions in

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OCD. In contrast, the hippocampus has not been the focus of OCD psychopathophysiology up to now. Its volume, however, is frequently found to be decreased in other psychiatric disorders such as depression (Frodl and O'Keane, 2013; Malykhin and Coupland, 2015) and PTSD (Ahmed-Leitao et al., 2016; O'Doherty et al., 2015). One potential mechanism underlying volumetric changes in the hippocampus seems to be uncontrollable stress (i.e., stress perceived as distress) which is one of the main characteristics of many psychiatric disorders such as PTSD. Distress has been demonstrated to change neuronal morphology, suppress neuronal proliferation, and reduce hippocampal volume (Kim et al., 2015). According to ICD-10, OCD is classified as a stress-related disorder and patients with OCD tend to report high levels of stress and anxiety independent of their specific symptoms or symptom profiles (Stein et al., 2010). Therefore, there is strong reason to assume that hippocampal volume differences may be clinically relevant in OCD as well. Of note, the ENIGMA meta-analysis identified hippocampal volume differences to be larger in medicated patients, however, no relationship with symptoms was found. The ENIGMA study related volume differences to specific symptoms as assessed by the Y-BOCS checklist. However, it should be noted that the majority of all OCD patients are multi-symptomatic and the individual symptom profiles of OCD patients are heterogeneous to the extent that two patients may display different overlapping or even non-overlapping symptom patterns (Mataix-Cols et al., 2005). Hence, instead of correlating outcome measures with specific symptoms one at a time, it may be reasonable to adopt an approach that accounts for possible interrelations of different symptom dimensions in patients. The fact that Boedhoe et al. (2017) found no significant correlations between symptom dimensions and hippocampus volumes is striking given the clear involvement of volume differences in patients found in their study. One possible explanation might be that symptom dimensions were related to structural alterations while controlling for the effects of other symptom dimensions, therefore effectively treating each symptom in isolation. To find out more about the clinical relevance of the recently reported differences in hippocampal structure, the present study employs a cluster analysis approach on dimensional symptoms to reach a differentiation into distinct symptom composition profiles, comparing hippocampal volumes between the different symptom profile groups. Thus, we aimed at exploring whether taking into account the interrelation between different symptoms, i.e., patients´ symptom composition profile, would be a valuable approach to relate structural alterations to clinically relevant features. We assumed that if the hippocampus would indeed be differentially affected in dependence on specific symptom composition profiles volume differences should be related to different symptom profiles. If hippocampus volumes would not be related to symptom profiles, this would rather speak in favor of a clinically unspecific hippocampal involvement in the disease.

2. Methods and materials

2.1. Participants

Data from two samples were combined. Sample one (S1) comprised $n = 42$ patients and $n = 46$ healthy controls and sample two (S2) comprised $n = 24$ patients and $n = 20$ healthy controls resulting in a total size of $n = 66$ patients with OCD as the primary diagnosis according to DSM-IV criteria and $n = 66$ healthy controls (see Table 1 for demographic and clinical details). Patients and controls were matched for sex and age in both samples. All patients were recruited from the Windach Institute and Hospital of Neurobehavioural Research and Therapy, Germany, and diagnoses were made by an experienced psychiatrist. Exclusion criteria for all participants were a history of clinically important head injuries, seizures or neurological diseases. At time of the study, $n = 48$ patients were drug-naive or medication free for at least 3 weeks and $n = 30$ patients had one or more comorbid diagnoses. To assess clinical severity of obsessive-compulsive symptoms, patients were administered the self-rated version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989; Hand and Büttner-Westphal, 1991). The Obsession-Compulsion Inventory revisited (OCI-R) (Foa et al., 2002; Gonner et al., 2008) was administered to more specifically assess different symptom dimensions. Additionally, depressive symptoms were evaluated based on the Beck Depression Inventory (BDI-II) (Beck et al., 1996; Hautzinger et al., 2009) in patients of sample S1 and the Hamilton Depression Scale (HAM-D) (Hamilton, 1960) in patients of sample S2. The study was approved by the local Ethics Committee of the Klinikum rechts der Isar, München and was conducted in accordance with the Declaration of Helsinki.

Table 1
Demographic and clinical sample characteristics.

Characteristics	OCD	HC
	n	*n*
	Mean ± SD	Mean ± SD
Sample size	66	66
Female	46 (69.7%)	46 (69.7%)
Age (years)	32.4 ± 10.5	31.6 ± 10.3‡
Disease duration	16.0 ± 10.8	
Y-BOCS total	21.0 ± 6.2	
Obsession	11.0 ± 3.6	
Compulsions	9.9 ± 3.9	
OCI-R total	25.4 ± 10.0	
Hoarding	2.3 ± 2.6	
Checking	5.5 ± 3.6	
Ordering	3.9 ± 3.8	
Neutralizing	2.2 ± 2.9	
Washing	4.8 ± 3.9	
Obsessing	6.8 ± 3.6	
BDI (S1)	18.0 ± 11.5	
HAM-D (S2)	12.6 ± 4.9	
Comorbidities	30 (45.5%)	
Depression	23	
Anxiety disorder	10	
Personality disorder	4	
Eating disorder	2	
ADHD	2	
Medication	48 (72.7%)	
SSRI	35	
SSRNI	6	
Neuroleptic	5	
TCA	3	
Methylphenidate	1	
Benzodiazepine	1	
NDRI	1	
NaSSA	1	

Note that multiple comorbid diagnoses as well as different medication types can be present in a single patient; abbreviations for medication: NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine-dopamine reuptake inhibitor; SSNRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

‡ Two-sample *t*-test ($t(130) = 0.442$, $p = 0.659$).

2.2. Image acquisition

Magnetic resonance imaging was conducted on a 3T Philips Ingenia (Philips Healthcare, Best, The Netherlands) using a 12-channel (SENSE) head coil. For sample S1, structural imaging consisted of a T1-weighted 3D MPRAGE sequence with an isotropic resolution of 1 mm (170 slices, sagittal orientation, 240 × 240 matrix, TR = 9 ms, TE = 4 ms, flip angle = 8°) while for sample S2, imaging consisted of a T1-weighted 3D MPRAGE sequence with a resolution of 0.7 × 0.75 × 0.7 mm (230 slices, sagittal orientation, 368 × 340 matrix, TR = 11 ms, TE = 5.1 ms, flip angle = 8°). Prior to analysis the 24 submillimeter data sets of sample S2 were downsampled in order for all images to have a consistent resolution of 1 mm isotropic.