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（強迫性障害における symptom dimension と脳形態との関連）

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廣瀬　素久

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Relationship between symptom dimensions and brain morphology in obsessive-compulsive disorder

Motohisa Hirose, M.S.[1,2], Yoshiyuki Hirano, Ph.D.[1,2], Kiyotaka Nemoto, M.D., Ph.D.[3], Chihiro Sutoh, M.D., Ph.D.[4], Kenichi Asano, Ph.D.[1,2], Haruko Miyata, M.A.[1], Junko Matsumoto, Ph.D.[5], Michiko Nakazato, M.D., Ph.D.[1,2], Koji Matsumoto, A.S.[6], Yoshitada Masuda, Ph.D.[6], Masaomi Iyo, M.D., Ph.D.[7], Eiji Shimizu, M.D., Ph.D.[1,2,4], Akiko Nakagawa, M.D., Ph.D.[1,2]

[1]Research Center for Child Mental Development, Chiba University, Chiba, Japan

[2]United Graduate School of Child Development, Osaka University, Kanazawa University, Hamamatsu University School of Medicine, Chiba University and University of Fukui, Suita, Osaka, Japan

[3]Department of Psychiatry, Division of Clinical Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

[4]Department of Cognitive Behavioral Physiology, Graduate School of Medicine, Chiba University, Chiba, Japan

[5]Department of Regional Disaster Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan

[6]Department of Radiology, Chiba University Hospital, Chiba, Japan

[7]Department of Psychiatry, Graduate School of Medicine, Chiba University, Chiba, Japan

Corresponding Author: Yoshiyuki Hirano, Ph.D.

Research Center for Child Mental Development, Chiba University
1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
Tel: +81-43-226-2974 Fax: +81-43-226-8588
E-mail: hirano@chiba-u.jp

ABSTRACT

Obsessive-compulsive disorder (OCD) is known as a clinically heterogeneous disorder characterized by symptom dimensions. Although substantial numbers of neuroimaging studies have demonstrated the presence of brain abnormalities in OCD, their results are controversial. The clinical heterogeneity of OCD could be one of the reasons for this. It has been hypothesized that certain brain regions contributed to the respective obsessive-compulsive dimensions. In this study, we investigated the relationship between symptom dimensions of OCD and brain morphology using voxel-based morphometry to discover the specific regions showing alterations in the respective dimensions of obsessive-compulsive symptoms. The severities of symptom dimensions in thirty-three patients with OCD were assessed using Obsessive-Compulsive Inventory-Revised (OCI-R). Along with numerous MRI studies pointing out brain abnormalities in autistic spectrum disorder (ASD) patients, a previous study reported a positive correlation between ASD traits and regional gray matter volume in the left dorsolateral prefrontal cortex and amygdala in OCD patients. We investigated the correlation between gray and white matter volumes at the whole brain level and each symptom dimension score, treating all remaining dimension scores, age, gender, and ASD traits as confounding covariates. Our results revealed a significant negative

correlation between washing symptom dimension score and gray matter volume in the right thalamus and a significant negative correlation between hoarding symptom dimension score and white matter volume in the left angular gyrus. Although our result was preliminary, our findings indicated that there were specific brain regions in gray and white matter that contributed to symptom dimensions in OCD patients.

Keywords: obsessive-compulsive disorder, voxel-based morphometry, Obsessive-Compulsive Inventory-Revised, washing symptom, hoarding symptom, thalamus

Introduction

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder consisting of unwanted thoughts (obsessions) and/or repetitive behaviors (compulsions) (Pauls, Abramovitch, Rauch, & Geller, 2014). The lifetime prevalence of OCD is reported to be 1.6-2.3% (Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Ruscio, Stein, Chiu, & Kessler, 2010), and it has been considered one of the leading causes of life disturbance (Michaud et al., 2006). Substantial numbers of neuroimaging studies have demonstrated the presence of brain abnormalities in OCD (Menzies et al. 2008; Nakao et al. 2014; Peng et al. 2012; Piras et al. 2013, 2015; Radua and Mataix-Cols 2009). The most widely accepted model of OCD proposes that abnormalities of the fronto-striatal circuit, involving the frontal cortex, anterior cingulate cortex (ACC), striatum, and thalamus, play an important role in its pathophysiology (Cummings, 1993; Graybiel & Rauch, 2000; Menzies et al., 2008; Milad & Rauch, 2012; Saxena, Brody, Schwartz, & Baxter, 1998). Furthermore, recent evidence has implicated abnormalities in additional brain regions involving the angular and supramarginal gyri, parietal lobe, insula, occipital lobe, and cerebellum in OCD patients (Menzies et al., 2008; Nishida et al., 2011; Piras et al., 2015; Song et al., 2011). These findings indicate that the pathophysiology of OCD involves a widespread neural network.

OCD is also well known as a clinically heterogeneous disorder that would be better understood as a dimensional disorder consisting of multiple overlapping obsessive-compulsive (OC) symptom dimensions (Mataix-Cols, do Rosario-Campos, & Leckman, 2005). Additionally, it is speculated that one of the reasons for the inconsistency of neuroimaging findings of OCD (Piras et al., 2015) is its clinical heterogeneity. Several studies have used voxel-based morphometry (VBM) to investigate the association between symptom dimensions and gray and white matter volume in OCD (Alvarenga et al. 2012; Gilbert et al. 2008; van den Heuvel et al. 2009; Lázaro et al. 2014a, 2014b; Pujol et al. 2004; Valente et al. 2005), but their results were inconsistent in respect to the relationship between OC symptom dimensions and gray and white matter volumes. From a clinical point of view, OCD patients have tended to present plural OC symptom dimensions in conjunction with their particular severity profile. This means that it is necessary to consider all OC symptoms together when accumulating data for OCD research.

Brain alterations due to the coexistence of depression symptoms and age at onset were reported in some studies in OCD patients. Cardoner et al. (2007) reported that lifetime major depressive disorder contributed to gray matter volume alterations in OCD patients. Christian et al. (2008) reported that OCD patients showed significantly larger gray matter volume in the left thalamus and also that OCD patients without major depression showed larger gray matter volume in the bilateral thalamus and left orbitofrontal cortex compared with healthy controls. As for brain abnormality associated with different age at onset, Rosso et al. (2014) suggested that age at onset may be a moderator of some of the white matter changes in pediatric OCD, and Busatto et al. (2001) found differences in regional cerebral blood flow between early onset OCD patients and late onset OCD patients. More recently, in terms of the presence of comorbid autistic spectrum disorders (ASD) in OCD, Cath et al. (2008) reported phenomenological overlapping between comorbid ASD and pure OCD in autistic phenomena by using Autism-Spectrum Quotient (AQ) (one of the screening tools of ASD; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) subscales. Also, a previous study reported that ASD patients showed structural brain alterations in the lateral occipital lobe, pericentral region, medial temporal lobe, basal ganglia, and proximate to the right parietal operculum (Nickl-Jockschat et al., 2012). Based on these reports, in a previous study from our team, Kobayashi et al. (2015) investigated the correlations between AQ scores and regional gray matter volumes in patients with OCD. They found a positive correlation between AQ scores and regional gray matter volume in the left dorsolateral prefrontal cortex (DLPFC) and amygdala.

Considering these findings, we hypothesized that gray and white matter volumes in specific brain regions contributed to each of the obsessive-compulsive symptom dimensions. To investigate the relationship between gray and white matter volume and symptom dimensions of OCD while taking into account the effects of ASD traits, we applied all severity scores of OC dimensions of OCI-R simultaneously and AQ scores as covariates using VBM.

Methods

Subjects

Patients were recruited from outpatients of Chiba University Hospital, Japan. All patients were diagnosed as OCD by a trained interviewer using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (Spitzer, Gibbon, & Williams, 1997). We employed the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989) for assessment of OC symptom severity. We also employed OCI-R to determine the profiles of the six OC symptom dimensions of each patient (washing, checking, ordering, obsessing, hoarding, and neutralizing; the severity of each dimension was assessed on a scale of 0 to 12). Patients with a Y-BOCS score of 16 or higher and a total intelligence quotient (IQ) of 80 or higher as assessed by Wechsler

Adult Intelligence Scale (WAIS-III) (Wechsler, 1997) were included. The patients ranged in age from 18 to 48 years. Exclusion criteria were neurological disorders, schizophrenia and related disorders including delusional disorder or psychotic disorders, substance dependencies, organic brain diseases, and severe physical diseases. Handedness of the participants was determined by Edinburgh Handedness Inventory (Oldfield, 1971). We also measured ASD traits of patients using the AQ scale (Wakabayashi, Baron-Cohen, Wheelwright, & Tojo, 2006; Wakabayashi, Tojo, Baron-Cohen, & Wheelwright, 2004). The Institutional Research and Ethics Committee of the Graduate School of Medicine, Chiba University, approved the study (No. 1330), and written informed consent for the study was obtained from each subject before the assessments began. The trial was registered as UMIN000008765.

MRI acquisition

All subjects underwent T1-weighted MRI by scanner equipped with a 32-channel phased-array head coil (Discovery MR750 3.0T; GE Healthcare). Images were collected by 3D fast spoiled gradient-echo (FSPGR) sequence (echo time: 3.164 ms; repetition time: 8.124 ms; flip angle: 15°; acquisition matrix: 256 × 256; slice thickness: 1 mm; field of view: 25.6 × 25.6 cm^2; number of excitations: 1; bandwidth: 31.25 kHz; inversion time: 420 ms; acceleration factor: 2).

MRI data processing

We processed T1-weighted MR images using Statistical Parametric Mapping 8 (SPM8, Wellcome Institute of Neurology, University College London, UK) running under MATLAB R2013a (The MathWorks Inc., Natick, MA, USA). The VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/), which is an extension of the unified segmentation model consisting of spatial normalization, bias field correction, and tissue segmentation (Ashburner & Friston, 2005), was used for preprocessing the images. Registration to the stereotactic space of the Montreal Neurological Institute (MNI) consisted of linear affine transformation and nonlinear deformation using high-dimensional Diffeomorphic Anatomical Registration through Exponential Lie Algebra (DARTEL) normalization (Ashburner, 2007). The normalized and segmented images were modulated by applying a nonlinear deformation, which allows comparison of absolute amounts of tissue corrected for individual differences in brain size (Klein et al., 2009). Finally, bias-corrected, modulated, and warped tissue maps were smoothed with an 8-mm full width at half maximum Gaussian kernel. Voxel resolution of smoothed images was 1.5 × 1.5 × 1.5 mm.

Statistical analysis

Statistical analysis was also performed with SPM8, which implemented a general linear model. We investigated correlations between the score of each OC symptom dimension and the gray and white matter volume by multiple regression analysis. First, we performed whole-brain analysis to determine the correlation between OCI-R scores and gray and white matter volume in OCD patients. The significance level was initially set at $p < 0.001$ uncorrected for multiple comparisons. After that, each dimension analysis was reported as significant if the cluster size survived at $q < 0.05$, false discovery rate (FDR) corrected for multiple comparisons at the cluster level, and the cluster size was obtained after applying gray matter or white matter mask. We treated all of the remaining OCI-R scores as covariates for obtaining specific brain alterations in each symptom dimension. Further, gender, age, and AQ scores were used as covariates for all analyses to control for potentially confounding variables. The anatomic location of each resulting cluster was determined using the MRI Atlas (Oishi, Faria, Zijl, & Mori, 2010).

Results

Forty-four patients with OCD were initially entered into this study, but eleven were then excluded on the basis of the exclusion criteria. Thus, thirty-three patients were analyzed. Their detailed demographics are summarized in Table 1. We investigated the correlations between respective obsessive-compulsive symptom dimension scores and gray and white matter volumes in OCD patients in consideration of the effects of ASD traits. There was a significant negative correlation between washing scores and regional brain volumes in the right thalamus (peak MNI coordinates: x, 3; y, -18; z, 12; cluster size, 527; Fig. 1 and Table 2). Further, there was a significant negative correlation between hoarding scores and regional brain volumes in the left angular gyrus white matter (peak MNI coordinates: x, -42; y, -45; z, 33; cluster size, 1761; Fig. 2 and Table 2). As mentioned in the Introduction, comorbid depressive symptoms (as measured using the BDI) and age at OCD symptom onset may differentially affects brain morphology. Then, we analyzed the data using the BDI scores as a nuisance covariate in gray matter. We found a negative correlation between washing dimension score and the volume of the left superior temporal gyrus, left thalamus, and the left postcentral gyrus in addition to the right thalamus, the same result as before using BDI scores as a nuisance covariate (Fig. S1 and Table S1). In terms of white matter, only cluster size and peak MNI coordinates were changed from 1761 (x, -42; y, -45; z, 33) to 1229 (x, -42; y, -43; z, 31) in angular gyrus white matter, the same region as before using the BDI scores. In addition, we analyzed the data using onset as a nuisance covariate in gray matter. As a result, only cluster size was changed from 527 to 493 in the right thalamus.

Discussion

To our knowledge, this is the first study to investigate the relationship between OC symptom dimensions and brain morphometry while considering the influence of age, gender, other OC symptom dimensions and ASD traits. Focusing on symptom dimensions to investigate the clinical heterogeneity of OCD in this study, we found significant correlations between washing scores and gray matter volumes in the right thalamus (Fig. 1 and Table 2) and between hoarding scores and volumes in the left angular gyrus white matter (Fig. 2 and Table 2). As far as we know, no studies had taken into consideration the influence of the severity scores of the other OC symptom dimensions using OCI-R when investigating brain regions with gray and white matter volumes showing significant correlations with each symptom dimension score in a whole-brain analysis. The thalamus was identified as one of the important regions in the fronto-striatal circuit and is one node within a network implicated in the pathophysiology of OCD (Menzies et al., 2008; Saxena et al., 1998). The pathway projects from the cortex to the thalamus via the striatum and back to the cortex (Alexander, DeLong, & Strick, 1986). Dysfunction in this circuit has been considered to represent the pathophysiology of this disorder. Previous neuroimaging studies focusing on the OC symptom dimensions also investigated the relationship between this circuit and symptom dimensions. In the washing symptom dimension, several neuroimaging studies have reported these brain abnormalities. Lázaro et al. (2014a) found that fractional anisotropy was significantly decreased in the thalamus in patients with a predominant contamination/washing dimension in a diffusion tensor imaging study. They discovered abnormalities in the microstructure of white matter in a putative limbic-cortical-striatal-thalamic circuit. Also, a functional MRI (fMRI) study found decreased activation in the thalamus in patients with OCD compared to controls when contamination-relevant stimuli were provoked (Gilbert et al. 2009). A perfusion-weighted imaging study in unmedicated OCD patients with contamination/washing symptom suggested that regional cerebral blood flow was significantly increased after symptom-provocation task in the thalamus (Chen, Xie, Han, Cui, & Zhang, 2004). However, there have been no morphometric studies to show the relationship between washing symptom dimension and thalamus. Therefore, our investigation provided additional evidence for the relationship between washing symptom dimension and thalamus volume, and this was in accordance with previous DTI, fMRI, and perfusion-weighted imaging studies. Those studies suggested that OCD patients with washing/contamination symptom have functional and morphometric alterations in the thalamus. Previously, three research groups investigated the relationship between washing dimension and brain regions using VBM. Those studies did not report the thalamus, but various other brain regions related to washing dimension. Okada et al. (2015) reported that washing dimension scores were negatively correlated with gray matter volume in the right insula and positively correlated with gray matter volume in the right cerebellar tonsil. van den Heuvel et al. (2009) showed significant negative correlation in the bilateral caudate. Gilbert et al. (2008) reported significant negative correlation in right Brodmann area 6. Okada et al. (2015) and van den Heuvel et al. (2009) employed different assessment scales, the symptom checklist of the Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989), and Dimensional Yale-Brown Obsessive-Compulsive Scale (Rosario-Campos et al., 2006) and Padua Inventory-Revised (Sanavio, 1988; Van Oppen, Hoekstra, & Emmelkamp,

1995) assessment scale, respectively. Gilbert et al. (2008) conducted multivariate regression analysis including the brain region volumes that were identified in the comparison between OCD patients and healthy controls. Those methodological differences might have led to the distinctions in the results.

In clinical scenarios, OCD patients with contamination/washing symptoms harbor obsessions that they might have touched objects even when they have simply glimpsed the objects. These obsessions increase and induce compulsions such as washing hands repeatedly. Rauch et al. advocated that the obsessions represent failures in filtering at the level of the thalamus, attributed to deficient modulation of the cortico-striato-thalamic collateral pathway (Rauch et al. 2002). They claimed that compulsion is induced when the information that is normally processed efficiently outside of the conscious domain instead finds access to the explicit processing system because of striatal dysfunction. As a result, striato-thalamic modulation might have occurred via performance such as ritualized thoughts or behaviors that activate the adjacent, intact striato-thalamic network. This compensatory function is used to explain the reason for the numerous repetitive behaviors required until the precipitating obsessions settle down. To view our result in terms of this theory, the decreasing thalamic volume in OCD patients with washing dimension might be associated with the normal striato-thalamic network function against cognitive intrusion such as related fear of contamination. Further, the prefrontal cortex was indicated as the region being involved with emotional behaviors such as disgust (Lawrence et al., 2007). In addition, significantly higher fractional anisotropy in bilateral prefrontal white matter was shown in patients with a predominant contamination/cleaning symptom dimension (Ha et al., 2009). Therefore, we could also expect alteration of the prefrontal cortex in OCD patients who had the washing dimension. The reason why we found a correlation with the washing dimension score in the thalamus but not in the prefrontal cortex might have been caused by excluding the effect of other dimensions by treating the remaining five dimension scores as nuisance covariates. Also, our small sample size could have induced these results. Although our study did not identify the thalamus as the region most responsible for the washing dimension, the thalamus might be involved in the compulsion, such as repetitive hand washing. Then, we also analyzed the data with the addition of the BDI scores (n=28 out of 33) as a nuisance covariate. In gray matter analysis, we found a negative correlation between washing dimension scores and the volume of the left superior temporal gyrus, left thalamus, and left postcentral gyrus in addition to the right thalamus (Fig. S1 and Table S1). This result, namely, that more negative correlations in thalamus volume were shown by excluding the effect of depression, supported the previous studies (Kong et al., 2014; W. Peng, Chen, Yin, Jia, & Gong, 2016). They reported increased gray matter volume in the left (Kong et al., 2014) or bilateral (W. Peng et al., 2016) thalamus in medication-naive major depression disorder compared with HC. Furthermore, an additional result of the involvement of the superior temporal gyrus in the pathophysiology of OCD was consistent with previous reports (Choi et al., 2006; Nakamae et al., 2012a; Tang et al., 2015). Nakamae et al. (2012) reported reduced cortical thickness, and Choi et al. (2006) and Tang et al. (2015) reported significantly smaller gray matter volume in the superior temporal gyrus compared with healthy controls. Although our sample size was small, the result suggested that the involvement of thalamus in the washing symptom dimension in OCD patients exists with or without the comorbidity of depression.

On the other hand, there has been no other report regarding angular gyrus white matter showing a significant negative correlation with hoarding dimension scores. Piras et al. (2015), however, reported in a meta-analysis of DTI studies that altered anatomical connectivity between frontal and parieto-occipital associative cortices might be related to the pathophysiology of OCD. Our result with angular gyrus white matter could support this notion. With regard to gray matter studies, Rauch et al. (1994) showed involvement of the angular gyrus with a symptom-provocation PET study of

OCD. Also, Valente et al. (2005) found decreased right angular and supramarginal gyrus volumes in OCD patients. From those studies, Menzies et al. (2008) indicated the existence of extra brain regions involved in OCD in addition to the fronto-striatal circuit. They suggested that parietal lobe dysfunction particularly within the angular gyrus could be related to the cognitive impairment in OCD. According to symptomatology, hoarding symptom showed various cognitive deficits. Then, the parietal lobe including the angular gyrus might contribute to the cognitive deficit events of hoarding symptom such as the excessive acquisition of and inability to discard objects (Tolin et al., 2012). As for hoarding dimension, Gilbert et al. (2008) indicated that gray matter volume in left Brodmann area 6 decreased with hoarding scores, and Mataix-Cols et al. (2004) reported significantly greater activation in the left precentral gyrus and right orbitofrontal cortex compared with healthy controls. Based on these studies, involvement of the fronto-striatal circuit in hoarding dimensions was actually preconceived. Nevertheless, our result showed the correlation between hoarding dimension scores and brain volumes in angular gyrus white matter. This result might also have been influenced by our nuisance covariates and small sample size.

There are several limitations to our study. First, the patient sample may not have been large enough to allow us to detect robust correlations between symptom dimension scores and gray and white matter volumes in brain regions. This might be one of the reasons for the correlations being detected in only one dimension each in gray and white matter. Second, 81% of our participants were taking medications. Previous studies have reported medication effects on brain structures including the thalamus in OCD (Gilbert et al. 2000; Hoexter et al. 2012; Valente et al. 2005). Finally, our sample included OCD patients with comorbid diseases. Future studies focusing on OC symptom dimensions with larger numbers of treatment-naive subjects and less comorbidity might elucidate the pathophysiology of OCD.

In conclusion, we found significant correlations between washing dimension scores and gray matter volumes in the right thalamus and between hoarding dimension and brain volume in left angular gyrus white matter while treating the remaining five dimension scores, gender, age, and AQ scores as nuisance covariates. Although our results were preliminary, we found a particular relation between a symptom dimension and the respective brain region. While searching for the dysfunction of neural circuits, it is important to observe regions playing a major role in each symptom dimension for a better understanding of the pathophysiology of this disabling disorder.

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Disclosure Statement

The authors declare that they have no conflict of interest.

Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

References

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience*, *9*, 357–381. http://doi.org/10.1146/annurev.ne.09.030186.002041

Alvarenga, P. G., do Rosário, M. C., Batistuzzo, M. C., Diniz, J. B., Shavitt, R. G., Duran, F. L. S., … Hoexter, M. Q. (2012). Obsessive-compulsive symptom dimensions correlate to specific gray matter volumes in treatment-naïve patients. *Journal of Psychiatric Research*, *46*(12), 1635–1642. http://doi.org/10.1016/j.jpsychires.2012.09.002

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. http://doi.org/10.1016/j.neuroimage.2007.07.007

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*(3), 839–851. http://doi.org/10.1016/j.neuroimage.2005.02.018

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, *31*(1), 5–17.

Busatto, G. F., Buchpiguel, C. A., Zamignani, D. R., Garrido, G. E., Glabus, M. F., Rosario-Campos, M. C., … Miguel, E. C. (2001). Regional cerebral blood flow abnormalities in early-onset obsessive-compulsive disorder: an exploratory SPECT study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*(3), 347–354. http://doi.org/10.1097/00004583-200103000-00015

Cardoner, N., Soriano-Mas, C., Pujol, J., Alonso, P., Harrison, B. J., Deus, J., … Vallejo, J. (2007). Brain structural correlates of depressive comorbidity in obsessive–compulsive disorder. *NeuroImage*, *38*(3), 413–421. http://doi.org/10.1016/j.neuroimage.2007.07.039

Cath, D. C., Ran, N., Smit, J. H., van Balkom, A. J. L. M., & Comijs, H. C. (2008). Symptom overlap between autism spectrum disorder, generalized social anxiety disorder and obsessive-compulsive disorder in adults: a preliminary case-controlled study. *Psychopathology*, *41*(2), 101–110. http://doi.org/10.1159/000111555

Chen, X.-L., Xie, J.-X., Han, H.-B., Cui, Y.-H., & Zhang, B.-Q. (2004). MR perfusion-weighted imaging and quantitative analysis of cerebral hemodynamics with symptom provocation in unmedicated patients with obsessive-compulsive disorder. *Neuroscience Letters*, *370*(2–3), 206–211. http://doi.org/10.1016/j.neulet.2004.08.019

Choi, J.-S., Kim, H.-S., Yoo, S. Y., Ha, T.-H., Chang, J.-H., Kim, Y. Y., … Kwon, J. S. (2006). Morphometric alterations of anterior superior temporal cortex in obsessive-compulsive disorder. *Depression and Anxiety*, *23*(5), 290–296. http://doi.org/10.1002/da.20171

Christian, C. J., Lencz, T., Robinson, D. G., Burdick, K. E., Ashtari, M., Malhotra, A. K., … Szeszko, P. R. (2008). Gray matter structural alterations in obsessive–compulsive disorder: Relationship to neuropsychological functions. *Psychiatry Research: Neuroimaging*, *164*(2), 123–131. http://doi.org/10.1016/j.pscychresns.2008.03.005

Cummings, J. L. (1993). Frontal-subcortical circuits and human behavior. *Archives of Neurology*, *50*(8), 873–880.

Gilbert, A. R., Akkal, D., Almeida, J. R. C., Mataix-Cols, D., Kalas, C., Devlin, B., … Phillips, M. L. (2009). Neural correlates of symptom dimensions in pediatric obsessive-compulsive disorder: a functional magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(9), 936–944. http://doi.org/10.1097/CHI.0b013e3181b2163c

Gilbert, A. R., Mataix-Cols, D., Almeida, J. R. C., Lawrence, N., Nutche, J., Diwadkar, V., … Phillips, M. L. (2008a). Brain structure and symptom dimension relationships in obsessive-compulsive disorder: a voxel-based morphometry study. *Journal of Affective Disorders*, *109*(1–2), 117–126. http://doi.org/10.1016/j.jad.2007.12.223

Gilbert, A. R., Mataix-Cols, D., Almeida, J. R. C., Lawrence, N., Nutche, J., Diwadkar, V., … Phillips, M. L. (2008b). Brain structure and symptom dimension relationships in obsessive–compulsive disorder: A voxel-based morphometry study. *Journal of Affective Disorders*, *109*(1–2), 117–126. http://doi.org/10.1016/j.jad.2007.12.223

Gilbert, A. R., Moore, G. J., Keshavan, M. S., Paulson, L. A., Narula, V., Mac Master, F. P., … Rosenberg, D. R. (2000). Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. *Archives of General Psychiatry*, *57*(5), 449–456.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., … Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry*, *46*(11), 1006–1011.

Graybiel, A. M., & Rauch, S. L. (2000). Toward a neurobiology of obsessive-compulsive disorder. *Neuron*, *28*(2), 343–347.

Ha, T. H., Kang, D.-H., Park, J. S., Jang, J. H., Jung, W. H., Choi, J.-S., … Kwon, J. S. (2009). White matter alterations in male patients with obsessive-compulsive disorder. *Neuroreport*, *20*(7), 735–739. http://doi.org/10.1097/WNR.0b013e32832ad3da

Heuvel, O. A. van den, Remijnse, P. L., Mataix-Cols, D., Vrenken, H., Groenewegen, H. J., Uylings, H. B. M., … Veltman, D. J. (2009). The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain*, *132*(4), 853–868. http://doi.org/10.1093/brain/awn267

Hoexter, M. Q., de Souza Duran, F. L., D'Alcante, C. C., Dougherty, D. D., Shavitt, R. G., Lopes, A. C., … Busatto, G. F. (2012). Gray matter volumes in obsessive-compulsive disorder before and after fluoxetine or cognitive-behavior therapy: a randomized clinical trial. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *37*(3), 734–745. http://doi.org/10.1038/npp.2011.250

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617–627. http://doi.org/10.1001/archpsyc.62.6.617

Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M.-C., … Parsey, R. V. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *NeuroImage*, *46*(3), 786–802. http://doi.org/10.1016/j.neuroimage.2008.12.037

Kobayashi, T., Hirano, Y., Nemoto, K., Sutoh, C., Ishikawa, K., Miyata, H., … Nakagawa, A. (2015). Correlation between Morphologic Changes and Autism Spectrum Tendency in Obsessive-Compulsive Disorder. *Magnetic Resonance in Medical Sciences: MRMS: An Official Journal of Japan Society of Magnetic Resonance in Medicine*, *14*(4), 329–335. http://doi.org/10.2463/mrms.2014-0146

Kong, L., Wu, F., Tang, Y., Ren, L., Kong, D., Liu, Y., … Wang, F. (2014). Frontal-subcortical volumetric deficits in single episode, medication-naïve depressed patients and the effects of 8 weeks fluoxetine treatment: a VBM-DARTEL study. *PloS One*, *9*(1), e79055. http://doi.org/10.1371/journal.pone.0079055

Lawrence, N. S., An, S. K., Mataix-Cols, D., Ruths, F., Speckens, A., & Phillips, M. L. (2007). Neural responses to facial expressions of disgust but not fear are modulated by washing symptoms in OCD. *Biological Psychiatry*, *61*(9), 1072–1080. http://doi.org/10.1016/j.biopsych.2006.06.033

Lázaro, L., Calvo, A., Ortiz, A. G., Ortiz, A. E., Morer, A., Moreno, E., … Bargallo, N. (2014). Microstructural brain abnormalities and symptom dimensions in child and adolescent patients with obsessive-compulsive disorder: a diffusion tensor imaging study. *Depression and Anxiety*, *31*(12), 1007–1017. http://doi.org/10.1002/da.22330

Lázaro, L., Ortiz, A. G., Calvo, A., Ortiz, A. E., Moreno, E., Morer, A., … Bargallo, N. (2014). White matter structural alterations in pediatric obsessive-compulsive disorder: relation to symptom dimensions. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *54*, 249–258. http://doi.org/10.1016/j.pnpbp.2014.06.009

Mataix-Cols, D., do Rosario-Campos, M. C., & Leckman, J. F. (2005). A Multidimensional Model of Obsessive-Compulsive Disorder. *American Journal of Psychiatry*, *162*(2), 228–238. http://doi.org/10.1176/appi.ajp.162.2.228

Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, & Phillips ML. (2004). DIstinct neural correlates of washing, checking, and hoarding symptomdimensions in obsessive-compulsive disorder. *Archives of General Psychiatry*, *61*(6), 564–576. http://doi.org/10.1001/archpsyc.61.6.564

Menzies, L., Chamberlain, S. R., Laird, A. R., Thelen, S. M., Sahakian, B. J., & Bullmore, E. T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited. *Neuroscience & Biobehavioral Reviews*, *32*(3), 525–549. http://doi.org/10.1016/j.neubiorev.2007.09.005

Michaud, C. M., McKenna, M. T., Begg, S., Tomijima, N., Majmudar, M., Bulzacchelli, M. T., … Murray, C. J. L. (2006). The burden of disease and injury in the United States 1996. *Population Health Metrics*, *4*, 11. http://doi.org/10.1186/1478-7954-4-11

Milad, M. R., & Rauch, S. L. (2012). Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. *Trends in Cognitive Sciences*, *16*(1), 43–51. http://doi.org/10.1016/j.tics.2011.11.003

Nakamae, T., Narumoto, J., Sakai, Y., Nishida, S., Yamada, K., Kubota, M., … Fukui, K. (2012a). Reduced cortical thickness in non-medicated patients with obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *37*(1), 90–95. http://doi.org/10.1016/j.pnpbp.2012.01.001

Nakamae, T., Narumoto, J., Sakai, Y., Nishida, S., Yamada, K., Kubota, M., … Fukui, K. (2012b). Reduced cortical thickness in non-medicated patients with obsessive-compulsive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *37*(1), 90–95. http://doi.org/10.1016/j.pnpbp.2012.01.001

Nakao, T., Okada, K., & Kanba, S. (2014). Neurobiological model of obsessive-compulsive disorder: Evidence from recent neuropsychological and neuroimaging findings. *Psychiatry and Clinical Neurosciences*, 587–605. http://doi.org/10.1111/pcn.12195

Nickl-Jockschat, T., Habel, U., Michel, T. M., Manning, J., Laird, A. R., Fox, P. T., … Eickhoff, S. B. (2012). Brain structure anomalies in autism spectrum disorder--a meta-analysis of VBM studies using anatomic likelihood estimation. *Human Brain Mapping*, *33*(6), 1470–1489. http://doi.org/10.1002/hbm.21299

Nishida, S., Narumoto, J., Sakai, Y., Matsuoka, T., Nakamae, T., Yamada, K., … Fukui, K. (2011). Anterior insular volume is larger in patients with obsessive–compulsive disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(4), 997–1001. http://doi.org/10.1016/j.pnpbp.2011.01.022

Oishi, K., Faria, A. V., Zijl, P. C. M. van, & Mori, S. (2010). *MRI Atlas of Human White Matter, Second Edition* (2 edition). Academic Press.

Okada, K., Nakao, T., Sanematsu, H., Murayama, K., Honda, S., Tomita, M., … Kanba, S. (2015). Biological heterogeneity of obsessive-compulsive disorder: A voxel-based morphometric study based on dimensional assessment. *Psychiatry and Clinical Neurosciences*, *69*(7), 411–421. http://doi.org/10.1111/pcn.12269

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. http://doi.org/10.1016/0028-3932(71)90067-4

Pauls, D. L., Abramovitch, A., Rauch, S. L., & Geller, D. A. (2014). Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. *Nature Reviews Neuroscience*, *15*(6), 410–424. http://doi.org/10.1038/nrn3746

Peng, W., Chen, Z., Yin, L., Jia, Z., & Gong, Q. (2016). Essential brain structural alterations in major depressive disorder: A voxel-wise meta-analysis on first episode, medication-naive patients. *Journal of Affective Disorders*, *199*, 114–123. http://doi.org/10.1016/j.jad.2016.04.001

Peng, Z., Lui, S. S. Y., Cheung, E. F. C., Jin, Z., Miao, G., Jing, J., & Chan, R. C. K. (2012). Brain structural abnormalities in obsessive-compulsive disorder: Converging evidence from white matter and grey matter. *Asian Journal of Psychiatry*, *5*(4), 290–296. http://doi.org/10.1016/j.ajp.2012.07.004

Piras, F., Piras, F., Caltagirone, C., & Spalletta, G. (2013). Brain circuitries of obsessive compulsive disorder: a systematic review and meta-analysis of diffusion tensor imaging studies. *Neuroscience and Biobehavioral Reviews*, *37*(10 Pt 2), 2856–2877. http://doi.org/10.1016/j.neubiorev.2013.10.008

Piras, F., Piras, F., Chiapponi, C., Girardi, P., Caltagirone, C., & Spalletta, G. (2015). Widespread structural brain changes in OCD: a systematic review of voxel-based morphometry studies. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *62*, 89–108. http://doi.org/10.1016/j.cortex.2013.01.016

Pujol, J., Soriano-Mas, C., Alonso, P., Cardoner, N., Menchón, J. M., Deus, J., & Vallejo, J. (2004). Mapping structural brain alterations in obsessive-compulsive disorder. *Archives of General Psychiatry*, *61*(7), 720–730. http://doi.org/10.1001/archpsyc.61.7.720

Radua, J., & Mataix-Cols, D. (2009). Voxel-wise meta-analysis of grey matter changes in obsessive–compulsive disorder. *The British Journal of Psychiatry*, *195*(5), 393–402. http://doi.org/10.1192/bjp.bp.108.055046

Rauch, S. L., Corá-Locatelli, G., & Greenberg, B. D. (2002). Pathogenesis of obsessive-compulsive disorder. In *The American Psychiatric Publishing Textbook of Anxiety Disorders* (1st edition, pp. 191–205). Washington, DC: American Psychiatric Publishing, Inc.

Rauch, S. L., Jenike, M. A., Alpert, N. M., Baer, L., Breiter, H. C., Savage, C. R., & Fischman, A. J. (1994). Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Archives of General Psychiatry*, *51*(1), 62–70.

Rosario-Campos, M. C., Miguel, E. C., Quatrano, S., Chacon, P., Ferrao, Y., Findley, D., … Leckman, J. F. (2006). The Dimensional Yale–Brown Obsessive–Compulsive Scale (DY-BOCS): an instrument for assessing obsessive–compulsive symptom dimensions. *Molecular Psychiatry*, *11*(5), 495–504. http://doi.org/10.1038/sj.mp.4001798

Rosso, I. M., Olson, E. A., Britton, J. C., Stewart, S. E., Papadimitriou, G., Killgore, W. D., … Rauch, S. L. (2014). Brain white matter integrity and association with age at onset in pediatric obsessive-compulsive disorder. *Biology of Mood & Anxiety Disorders*, *4*(1), 13. http://doi.org/10.1186/s13587-014-0013-6

Ruscio, A. M., Stein, D. J., Chiu, W. T., & Kessler, R. C. (2010). The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Molecular Psychiatry*, *15*(1), 53–63. http://doi.org/10.1038/mp.2008.94

Sanavio, E. (1988). Obsessions and compulsions: the Padua Inventory. *Behaviour Research and Therapy*, *26*(2), 169–177.

Saxena, S., Brody, A. L., Schwartz, J. M., & Baxter, L. R. (1998). Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *The British Journal of Psychiatry. Supplement*, (35), 26–37.

Song, A., Jung, W. H., Jang, J. H., Kim, E., Shim, G., Park, H. Y., … Kwon, J. S. (2011). Disproportionate alterations in the anterior and posterior insular cortices in obsessive-compulsive disorder. *PloS One*, *6*(7), e22361. http://doi.org/10.1371/journal.pone.0022361

Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*. Washington DC: American Psychiatric Pub.

Tang, W., Huang, X., Li, B., Jiang, X., Li, F., Xu, J., … Gong, Q. (2015). Structural brain abnormalities correlate with clinical features in patients with drug-naïve OCD: A DARTEL-enhanced voxel-based morphometry study. *Behavioural Brain Research*, *294*, 72–80. http://doi.org/10.1016/j.bbr.2015.07.061

Tolin, D. F., Stevens, M. C., Villavicencio, A. L., Norberg, M. M., Calhoun, V. D., Frost, R. O., … Pearlson, G. D. (2012). Neural mechanisms of decision making in hoarding disorder. *Archives of General Psychiatry*, *69*(8), 832–841. http://doi.org/10.1001/archgenpsychiatry.2011.1980

Valente, A. A., Miguel, E. C., Castro, C. C., Amaro, E., Duran, F. L. S., Buchpiguel, C. A., … Busatto, G. F. (2005). Regional gray matter abnormalities in obsessive-compulsive disorder: a voxel-based morphometry study. *Biological Psychiatry*, *58*(6), 479–487. http://doi.org/10.1016/j.biopsych.2005.04.021

Van Oppen, P., Hoekstra, R. J., & Emmelkamp, P. M. (1995). The structure of obsessive-compulsive symptoms. *Behaviour Research and Therapy*, *33*(1), 15–23.

Wakabayashi, A., Baron-Cohen, S., Wheelwright, S., & Tojo, Y. (2006). The Autism-Spectrum Quotient (AQ) in Japan: A cross-cultural comparison. *Journal of Autism and Developmental Disorders*, *36*(2), 263–270. http://doi.org/10.1007/s10803-005-0061-2

Wakabayashi, A., Tojo, Y., Baron-Cohen, S., & Wheelwright, S. (2004). [The Autism-Spectrum Quotient (AQ) Japanese version: evidence from high-functioning clinical group and normal adults]. *Shinrigaku Kenkyu: The Japanese Journal of Psychology*, *75*(1), 78–84.

Wechsler, D. (1997). *WAIS-III: Administration and Scoring Manual*. New York: Harcourt Brace & Company.

Table 1. Clinical characteristics of patients with OCD

Variable	*N* (%)	Mean (SD)	Range
Age (years)		33.4 (7.7)	18-48
Gender (male/female)	12/21		
Handedness (right/left)	33/0		
Age at onset of OCD (years)		22.7 (7.8)	6-40
Duration of illness (years)		10.7 (7.9)	0-27
Y-BOCS		26.2 (3.5)	19-34
OCI-R Severity			
Washing	29 (88)	7.1 (4.5)	0-12
Checking	31 (94)	7.1 (3.6)	0-12
Ordering	30 (90)	3.2 (2.4)	0-9
Obsessing	33 (100)	8.8 (2.9)	1-12
Hoarding	26 (79)	4.1 (3.3)	0-10
Neutralizing	26 (79)	2.9 (3.0)	0-12
Total symptom severity		33.2 (8.4)	16-55
AQ		25.6 (7.2)	10-40
BDI[†]		16.9 (11.9)	2-44
FIQ		102.1 (11.4)	80-124
Comorbidities			
Major depressive disorder	7 (21)		
Social anxiety disorder	3 (9)		
Dysthymic disorder	1 (3)		
Generalized anxiety disorder	1 (3)		
Bulimia	1 (3)		
Agoraphobia	1 (3)		
Posttraumatic stress disorder	1 (3)		
Medication at time of study			
Medication-free	6 (18)		
SSRI	22 (67)		
Antipsychotic augmentations[‡]	7 (21)		
Major tranquilizers[‡]	11 (33)		
Clomipramine	3 (9)		

[†]Only 28 patients were assessed in the BDI sample.

[‡]Mean of chlorpromazine equivalent doses of major tranquilizers for each patient (87.9 ± 64.4 mg)

Abbreviations: AQ, Autism-Spectrum Quotient; BDI, Beck Depression Inventory; OCI-R, Obsessive-Compulsive Inventory-Revised; FIQ, Full scale Intelligence Quotient; OCD, obsessive-compulsive disorder; SD, standard deviation; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; SSRI, selective serotonin reuptake inhibitor

Table 2. Negative correlations between OCI-R variables and brain volumes in OCD patients.

Dimension	Brain region	Coordinates x	y	z	Z score	Cluster size
Gray matter						
Washing	R thalamus	3	-18	12	4.04	527
White matter						
Hoarding	L angular gyrus white matter	-42	-45	33	3.88	1761

Abbreviations: R, right; L, left

Results are shown at q < 0.05 considering a cluster-corrected false discovery rate (FDR) correction for multiple comparisons.

Table S1. Negative correlations between OCI-R variables and brain volumes, considering BDI scores as a nuisance covariate (n=28).

Dimension	Brain region	Coordinates			Z score	Cluster size
		x	y	z		
Gray matter						
Washing	L superior temporal gyrus	-53	2	1	4.7	410
	R thalamus	11	-33	0	4.51	910
	L thalamus	-8	-7	15	4.13	302
	L postcentral gyrus	-33	-30	52	3.97	277

Abbreviations: R, right; L, left

Results are shown at $q < 0.05$ considering a cluster-corrected false discovery rate (FDR) correction for multiple comparisons.

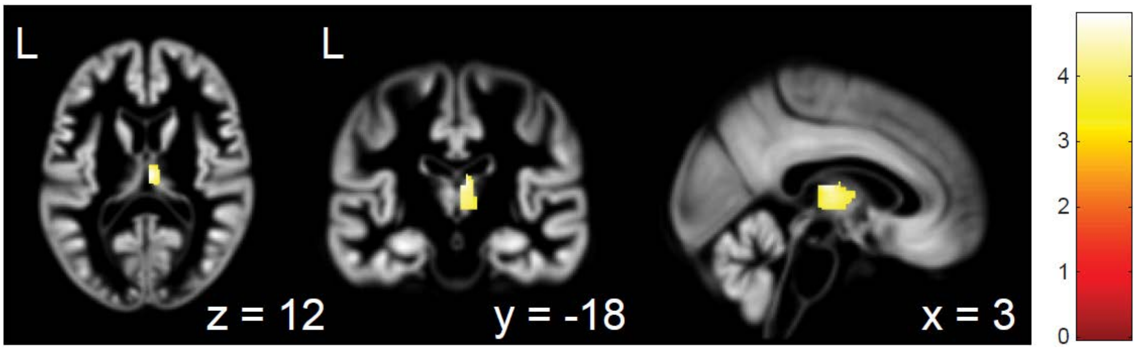

Figure 1. Correlations between washing symptom dimension scores and right thalamus volumes in OCD patients.

The negative correlation between regional gray matter volumes in the right thalamus and the washing dimension scores. Results are shown at $q < 0.05$, false discovery rate (FDR) corrected for multiple comparisons at the cluster level. Color bar shows t-value. Covariates are the remaining five dimension scores, gender, age, and AQ scores. L; left.

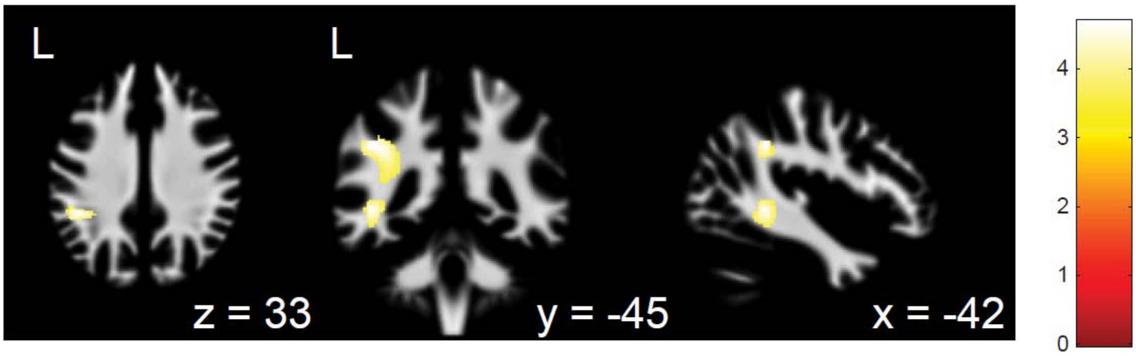

Figure 2. Correlations between hoarding symptom dimension scores and the left angular gyrus white matter volumes in OCD patients.

The negative correlation between regional white matter volumes in the left angular gyrus and the hoarding dimension scores. Results are shown at $q < 0.05$, false discovery rate (FDR) corrected for multiple comparisons at the cluster level. Color bar shows t-value. Covariates are the remaining five dimension scores, gender, age, and AQ scores. L; left.

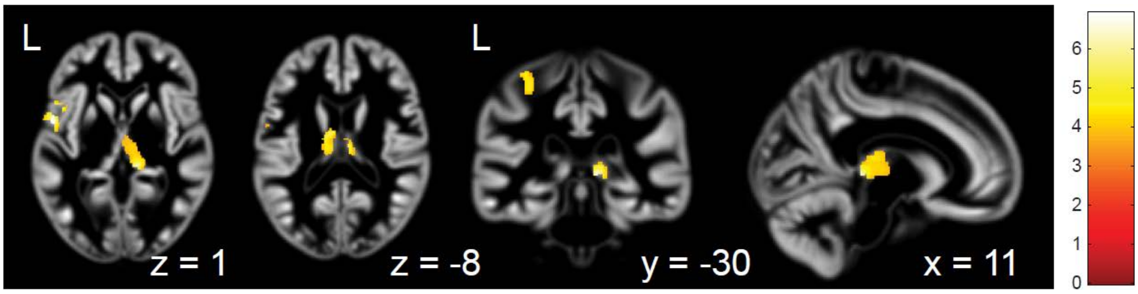

Figure S1. Negative liner correlations between OCI-R variables and gray matter volumes with the BDI scores as nuisance covariate (n=28).

The negative correlation between regional gray matter volumes in the superior temporal gyrus, right thalamus, left thalamus, and left postcentral gyrus, and the washing dimension scores. Results are shown at q < 0.05, false discovery rate (FDR) corrected for multiple comparisons at the cluster level. Color bar shows t-value. Covariates are the remaining five dimension scores, gender, age, AQ scores, and BDI scores. L; left.