A unique increase in prefrontal gray matter volume in hoarding disorder compared to obsessive-compulsive disorder

Satoshi Yamada¹, Tomohiro Nakao¹*, Keisuke Ikari¹, Masumi Kuwano¹, Keitaro Murayama¹, Hirofumi Tomiyama¹, Suguru Hasuzawa¹, Osamu Togao², Akio Hiwatashi², Shigenobu Kanba¹

¹ Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, 2 Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

* tomona@npsych.med.kyushu-u.ac.jp

Abstract

Background
Hoarding disorder (HD) is a disease concept newly presented in DSM-5. As far as we know, no studies have examined the structural changes relevant to hoarding by applying the diagnostic criteria of HD in DSM-5. In the present study, we aimed to find abnormalities in gray matter (GM) structures of patients with HD.

Methods
Seventeen patients who met the DSM-5 criteria for HD, 17 obsessive-compulsive disorder (OCD) patients, and 17 healthy controls (HCs) participated in this study. All participants underwent MRI scanning of the brain by a 3.0-Tesla MRI scanner. In a voxel-based morphometric procedure, preprocessed GM structural images were used to compare the three groups. Thereafter we investigated the correlation between the clinical data (age of onset, symptomatic severity) and GM volume.

Results
The HD group showed a significantly increased GM volume compared to the OCD and healthy control groups (p < 0.05) in both Brodmann area (BA)10 and BA11. There was no significant difference between OCD and healthy control groups. No significant correlation between the clinical data including age of onset, symptom severity score, and GM volume was observed in HD and OCD groups.

Conclusions
The results might help to explain the inconsistency of previous studies. As with OCD, HD is considered to have cognitive dysfunction as its basis. This result is convincing after considering the clinical features of HD and suggested that structural abnormalities in the prefrontal regions might relate to the pathophysiology of HD.
Introduction

Hoarding disorder (HD) is a disease concept newly presented in DSM-5. Patients with HD find it difficult to throw away possessions, regardless of the actual value, and organize those things. As a result, the possessions overflow the living space, and hinder living functions. Extreme forms of this behavior can fill a living space and cause sanitation problems. Moreover, hoarding symptoms might cause injuries due to fires and collapse, which can have a great impact not only on the person themselves and their family but also on neighboring residents.

To date, the neurobiological mechanisms of HD haven’t been investigated in detail. A study of human brain lesions was suggested that damage in the prefrontal region was associated with collecting behavior[1]. Furthermore, several studies have reported a correlation between hoarding symptoms and specific brain regions using neuroimaging technology. Functional neuroimaging methods, a positron emission tomography research study, revealed that obsessive-compulsive disorder (OCD) patients with compulsive hoarding had significantly lower glucose metabolism in the posterior cingulate gyrus and cuneus than normal control subjects [2]. A functional magnetic resonance imaging (fMRI) study revealed that OCD patients who were asked to imagine discarding various items demonstrated significantly greater activation than controls in left precentral gyrus and right orbitofrontal cortex[3]. Another fMRI study reported that the OCD patients with prominent hoarding symptoms showed greater activation in the bilateral anterior ventromedial prefrontal cortex (VMPFC) than patients without hoarding symptoms and healthy controls in response to a hoarding-related anxiety provocation[4]. During a hoarding-relevant decision-making task, patients with hoarding symptoms who met the clinical criteria of HD outlined by Frost and Hartl[5] and proposed for DSM-5[6] exhibited a biphasic abnormality in the insula and anterior cingulate cortex (ACC) [7]. Furthermore, several structural studies using voxel-based morphometry (VBM) indicated the association between hoarding symptom scores in OCD and gray matter (GM) volume in the left caudate [8], the left Brodmann area(BA)6[9], the left lateral orbitofrontal cortex (OFC) and the right parahippocampal gyrus[10]. These findings, however, are inconsistent. In addition, most of the previous studies focused on compulsive hoarding as a subtype of OCD. Only one fMRI study reveals that HD patients, diagnosed by DSM-5 criteria, exhibited significantly greater activity than controls in the ACC and right dorsolateral prefrontal cortex during the conflict monitoring and response inhibition conditions in the Go/No-Go task[11]. There are, as far as we know, no studies that have examined the structural changes relevant to hoarding by applying the diagnostic criteria of HD in DSM-5.

In the present study, we aimed to find abnormalities in GM structures of patients with HD by using the criteria of HD in DSM-5. To our knowledge, this is the first VBM study targeting HD patients diagnosed with DSM-5 criteria. Although previous findings are inconsistent, we hypothesized that HD patients exhibit peculiar changes in GM volume in the prefrontal region compared to OCD patients and healthy controls because of its association with collecting behavior based on a previous human regional study[1].

Materials and methods

Seventeen patients who met DSM-5 criteria for HD, 17 OCD patients, and 17 healthy controls (HCS) participated in this study. OCD patients and HCs were matched by age and sex to HD patients. The patients with HD and OCD were recruited from outpatients and inpatients of the Department of Neuropsychiatry, Kyushu University Hospital, Japan, and the HCs were recruited from the local community. The study was approved by an ethics committee of Kyushu University and each participating patient provided written informed consent after receiving a complete description of the study, which was approved by the institutional review board.
Diagnoses of HD and OCD were confirmed using the Structured Interview for Hoarding Disorder (SIHD) [12] and the Structured Clinical Interview (SCID-I) of DSM-IV by trained psychiatrists, respectively. SIHD was obtained directly from the original authors and translated into Japanese. The HCs were without comorbid axis I diagnoses including HD and OCD and had no history of neurological illness, other disorders of the central nervous system, or history of substance abuse.

The HD patients were assessed for the severity of their hoarding symptom using the Saving Inventory-Revised (SI-R) [13] [14] and the Clutter Image Rating (CIR) [15]. The SI-R is a 23-item self-administered questionnaire requesting a response on a 0–4 scale (range 0–92). We used a Japanese version of SI-R translated by Tsuchiyagaito et al. [13]. The CIR is a visual assessment composed of a series of nine photographs that specifically assess the severity of clutter in the three main rooms (kitchen, living room, and bedroom) in a general home environment. Global symptom severity in OCD patients was assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [16]. The HD and OCD patients were also evaluated for obsessive-compulsive symptoms using the Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS) [17], which divides obsessive-compulsive symptoms into six distinct dimensions: aggression/checking, sexual/moral/religious, symmetry/ordering/counting, contamination/washing, hoarding and miscellaneous. Also, the patient groups completed the Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) to assess the severity of depression and anxiety.

In order to exclude secondary hoarding symptoms, OCD patients who showed any hoarding symptoms (i.e., patients whose hoarding symptom scores on DY-BOCS were not less than 1 point) were excluded from the study. Also, for the purpose of eliminating OCD patients with atypical pathology such as “not just right feeling” rather than anxiety, OCD patients with atypical symptoms (such as sexual/ moral/religious, symmetry/ordering/counting) as the main symptoms were excluded. OCD patients who had comorbid axis I diagnoses and histories of neurological illness, other disorders of the central nervous system, or substance abuse were excluded.

All participants underwent MRI scanning of the brain on a 3.0-Tesla MRI scanner (Achieva TX, Philips Healthcare, Best, The Netherlands) with an 8-channel head coil at the Department of Radiology, Kyushu University. T1-weighted images were acquired with a 3D T1-weighted turbo field echo sequence with the following parameters: repetition time (TR) = 8.2 ms, echo time (TE) = 3.8 ms, flip angle = 8°, matrix = 240×240, T1 inversion time = 1026 ms, field of view (FOV) = 240×240 mm, number of signal averages (NSA) = 1, slice thickness = 1 mm, number of slices = 190, and scan time = 320 s.

Acquired images were first converted from DICOM to NifTI-1 format by using the dcm2nii software at MIRcron (https://www.nitrc.org/projects/mricron). Preprocessing and quality check of data were performed with SPM12 software (Functional Imaging Laboratory, Wellcome Trust Centre for Neuroimaging, Institute of Neurology at University College London, UK; http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB R2011b (Mathworks Inc., Sherborn, MA, USA).

Prior to preprocessing, anterior commissure-posterior commissure orientation was conducted on all T1-weighted data. Each image was segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the segment function of SPM12. Subsequently, the segmented GM images were spatially normalized using the diffeomorphic anatomical registration through an exponentiated lie algebra (DARTEL) algorithm. DARTEL templates were generated from all the MR images of the participants. After spatial normalization, the GM images were modulated by Jacobian determinants, and smoothed with an 8 mm full width at
half maximum (FWHM) Gaussian kernel. For this preprocessing, default parameters were used except for the affine regularization. Because the subjects are all Japanese, we used the East Asian template for affine regularization. Total intracranial volume was calculated by summing up gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid volume using the “Tissue Volumes” function of SPM12.

We also calculated the regional gray matter volume in two regions of interest (ROIs). For this, we used normalized but not smoothed images because signal intensities can vary with smoothed images, resulting in inaccurate volume. ROIs were generated from the Automatic Anatomic Labeling (AAL) tool[18] [19] included in the Wake Forest University WFU PickAtlas[19]. We employed BA10 and BA11 as ROIs. We selected these areas in response to ANOVA results. We made masks of these regions using PickAtlas, and obtained the gray matter volume of each region using a Matlab script written by Ridgway (http://www.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m).

After preprocessing, voxel-based analysis of variance (ANOVA) was carried out in order to investigate the presence of regional GM volume differences among the three groups (HD, OCD and HCs) using SPM12. The subject’s age at the time of MRI scanning, sex and total intracranial volume (TIV) were entered as nuisance covariates.

Then, we conducted analysis of covariance (ANCOVA) to assess the regional gray matter volumes of the three groups (HD, OCD, HCs) using JMP® 13 (SAS Institute Inc., Cary, NC, USA).

Using the formula \( y_i = \beta_0 + \beta_1 G_1 + \beta_2 A_i + \beta_3 \text{Sex} + \beta_4 \text{TIV} + \epsilon_i \) in this general linear model, we set each regional volume \( y_i \) as the objective variable, and the main effect group \( G_i \), age \( A_i \), gender \( \text{Sex} \), and total intracranial volume \( \text{TIV} \) as covariates.

In addition, we conducted a complementary analysis that compared HD patients who didn’t have comorbid OCD to patients with OCD, to exclude the effects of comorbid OCD condition on HD.

Finally, in order to investigate the relationship between the clinical data (age of onset, symptomatic severity) and the gray matter volume, we conducted a correlation analysis secondarily. As indicators of symptom severity, the SI-R, CIR, and Hoarding dimension score of DY-BOCS were used for the HD patients. Similarly, aggression/checking and contamination/washing scores of DY-BOCS were used as a severity index for the OCD patients. We examined the correlation between each symptom severity index and gray matter volume, and the significance was confirmed by the Spearman’s rank correlation coefficient.

**Results**

Details of demographic and clinical data are shown in Table 1. There were no significant differences among HD patients, OCD patients, and HCs in age (HD: 43.9±11.5, OCD: 39.9±9.0, HCs: 42.4±10.4) and gender. Also, there was no difference in the degree of depression and anxiety between the HD and OCD groups. The HD patients showed significantly higher scores on the SI-R and CIR, which means that these HD patients had clinically definite hoarding symptoms. The HD group showed significantly higher hoarding scores on DY-BOCS, while the OCD group showed scores of zero for this dimension. The HD patients had several comorbidities, of which five patients had OCD, three ADHD, and two major depression. For oral administration, there were 10 antidepressants, 7 benzodiazepines, 4 antiepileptics and 2 antipsychotics.

In the results of VBM analyses, all three groups (HD, OCD, and HCs) exhibited the presence of significant regional GM volume differences in the right prefrontal regions, including the frontal pole (FP) and the orbitofrontal cortex (OFC). The initial voxel threshold was set to
0.001 uncorrected. Clusters were considered as significant when falling below a cluster-corrected p (FWE) = 0.05. The cluster size was 1228 voxels and p value was 0.004. Peak coordinates (Montreal Neurological Institute) were x = 20, y = 64, and z = -18 (Fig 1 and Table 2).

In the comparison of the three groups based on the gray matter volume obtained by ROI analysis, the HD group showed a significantly increased GM volume compared to the OCD group and the healthy control group (p < 0.05) in both BA10 and BA11. There was no significant difference between OCD and the healthy control group (Fig 2). In the complementary analysis that compared the HD group without OCD to the OCD group, the volume increase of the HD group in BA10 and BA11 remained significant. A correlation analysis that investigated the relationship between the clinical data and the gray matter volume revealed no significant correlation between the clinical data including age of onset and symptom severity scores, and GM volume in both HD and OCD groups (Fig 3).

Discussion

In the present study, we found that the HD patients showed an increased GM volume in the broad prefrontal regions including the FP and OFC compared with the OCD patients. On the other hand, a human lesion study[1] showed an association between the prefrontal region and collecting behavior. Actually, the relationship between brain function and volumetric change is still unknown. An et al. reported that the OCD patients with prominent hoarding symptoms showed greater activation in the bilateral anterior VMPFC (BA11/10) than patients without...
Although they found excessive activation in these regions, they noted that “dysfunction in these regions (regardless its cause) seems to be associated with abnormal hoarding behaviors”. Similarly, we think that it is still unknown how the increased GM volume in the prefrontal region is associated with dysfunction of the same site and hoarding behaviors. The FP (BA10) comprises the most anterior part of the frontal lobe. The FP is assumed to be related to various brain functions, such as multi-tasking[20], cognitive branching[21], prospective memory[22], conflict resolution[23], and selection of sub-goals[24]. As far as we know, there is no study of HD that found any anatomical abnormalities related to these cognitive dysfunctions. By using functional neuroimaging, Tolin et al. found that patients with hoarding symptoms showed biphasic abnormalities in the insula and prefrontal regions.

Table 2. Differences in GM volumes among three groups (HD, OCD, and HCs).

| Comparison | BA | Anatomical Region          | p value | Cluster size | Peak coordinates (x, y, z) |
|------------|----|---------------------------|---------|--------------|---------------------------|
| ANOVA      | 11 | R. superior frontal gyrus | 0.004   | 1228         | 20 64–18                 |

ANOVA, analysis of variance; BA, Brodmann area; HD, hoarding disorder; OCD, obsessive-compulsive disorder; HCs, healthy controls
In the comparison of the three groups based on the gray matter volume obtained by ROI analysis, the HD group showed significantly increased GM volumes compared to the OCD group and the healthy control group (p < 0.05) in both BA10 and BA11.
anterior cingulate cortex (ACC)[7]. However, they did not find functional abnormalities in the prefrontal regions due to the nature of the task they employed. Meanwhile, by examining the healthy human participants, Fleming et al. reported that GM volume in the right anterior FP involved in the ability of metacognition[25]. Schmitz et al. also suggested that a more accurate level of trait/ability-based insight was related to increased signal change in the right anterior dorsal prefrontal cortex in traumatic brain injury patients[26]. Our speculation is that the

Fig 3. The results of correlation analysis. No significant correlation between the DY-BOCS dimensional score (HD: hoarding score, OCD: contamination/washing score) and GM volume was observed in either the HD or OCD group.

https://doi.org/10.1371/journal.pone.0200814.g003
function of the right prefrontal cortex might be involved in insight as a kind of metacognition. It would be reasonable that function abnormality in this area also affects decision-making such as acquiring, organizing, and throwing away objects. We, however, need further examination.

OFC has been frequently suggested to be associated with the pathophysiology of OCD. Although one Mega-Analysis study [27] suggested that OCD patients had significantly smaller volumes of frontal gray and white matter bilaterally, the results in VBM studies so far are inconsistent. For example, several studies have indicated that OCD patients have a larger OFC compared to control groups [8] [28] [29], while other studies report a smaller OFC [30] [31] [32]. In the present study, the HD group showed a prominent increase of OFC volume compared to the OCD group. Perhaps this result might help to explain the inconsistency of previous studies for OCD. By using a neurocognitive task during fMRI, Tolin et al. found that OCD patients, but not HD patients, were characterized by excessive activity in the left and right orbitofrontal gyri [33]. Although OCD is recognized as a disease of strong heterogeneity, most previous studies have included various subtypes of OCD and analyzed them as one group. Thus, it is undeniable that a mixture of hoarding symptoms might have influenced the results of these studies. To the extent that we have investigated, past VBM studies included approximately 15% to 55% [8] [30] [32] [34] [35] [36] OCD patients with hoarding symptoms. Since having any hoarding symptoms has been considered a subtype of OCD until primary hoarding symptoms were defined as HD in DSM-5, there is a possibility that the primary and secondary hoarding symptoms of OCD were completely mixed as “OCD”. Therefore, our result showing a significant increase in the prefrontal region in HD compared to OCD without hoarding has important implications.

Like OCD, HD is considered to have cognitive dysfunction as the basis of the disease. In recent years, research findings on various cognitive dysfunctions and neural bases of HD have been accumulated. With regard to cognitive dysfunction, impairments in various areas such as attention, decision-making, categorization and verbal and nonverbal recall have been clarified [37] [38] [39] [40] [41]. This result is convincing after considering the clinical features of HD and suggests that the structural abnormality in the prefrontal regions might be related to the pathophysiology of HD.

Comparison between OCD patients and HCs showed no significant differences. The OCD patients participating in this study were selected from the OCD patients participating in a previous study [42] by our group. Our previous study showed that OCD patients have increased GM volume in left thalamus compared to healthy controls, and this result is consistent with previous findings. Therefore, several reasons, such as sample size and excluding OCD with hoarding symptoms, might have affected the results.

A correlation between clinical data and GM volume has been mentioned in previous studies. A mega-analysis study showed that adult OCD patients with an early onset exhibited larger pallidum volumes and patients with a late onset exhibited smaller hippocampal volumes than controls [43]. Likewise, the correlation between age of onset and GM volume was pointed out in our previous study [42]. Alvarenga et al. showed that scores on the “hoarding” dimension of DY-BOCS were positively correlated with GM volume in the left superior lateral OFC and negatively correlated in the right parahippocampal gyrus, while there was no correlation between contamination dimension and GM volume [10]. Meanwhile, no correlation between the clinical data, including age of onset and symptom severity scores and GM volume, was found in our study. This might be affected by differences such as sample size and comorbidity, as described later.

The criteria of hoarding disorder (HD) in the previous studies employed various diagnostic criteria such as the clinical criteria outlined by Frost and Hartl in 1996 and proposed for DSM-5 [7], lifetime hoarding symptoms on the Y-BOCS Symptom Checklist and scored above the
group median on the SI-R (SI-R>30) [4] and HD criteria in DSM-5[11]. Although they have not been unified, most of the previous studies recruited homogeneous subjects with hoarding and shared common recognition that HD has different pathology from typical OCD. Therefore, we thought that comparing our results with previous studies has a certain meaning to comprehend the pathology of HD.

Our study had several limitations. The hoarding sample was relatively small and had various comorbidities such as OCD, ADHD, and major depression. These comorbid disorders are suggested to cause specific volumetric changes. It is suggested that patients with major depression disorder have smaller volumes of specific regions, such as the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex, and gyrus rectus [44], and it is known that ADHD also shows a volume reduction in the right lentiform nucleus that is extended to the caudate nucleus [45]. We did not especially exclude patients with concurrent OCD. There were five patients with concurrent HD and OCD in this study, and it is undeniable that this might have certain effects on the results. Concerned with this limitation, we conducted a second analysis with pure HD patients without OCD and obtained results similar to the main analysis, suggesting that they had an increased volume of the prefrontal region compared to OCD without hoarding. A further increase in the sample size and analysis of unalloyed HD patients who are not complicated by OCD are needed in the future. Finally, we were not able to control the effects of drug therapy in this study. Many patients took medications such as antidepressants and benzodiazepines, so the effects might need to be considered.

Supporting information
S1 Appendix. The detailed information of HD patients.
(XLSX)
S2 Appendix. The detailed information of OCD patients.
(XLSX)
S3 Appendix. The detailed information of healthy controls.
(XLSX)
S1 Fig. The result of ANOVA with SPM software.
(PNG)

Acknowledgments
We were supported by a Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network) from the Ministry of Education, Science, Sports and Culture of Japan in terms of the analysis technique. Katherine Ono provided assistance with language.

Author Contributions
Conceptualization: Satoshi Yamada, Tomohiro Nakao.
Data curation: Satoshi Yamada, Keisuke Ikari, Masumi Kuwano, Osamu Togao, Akio Hiwatashi.
Formal analysis: Satoshi Yamada, Keisuke Ikari.
Funding acquisition: Tomohiro Nakao.
Investigation: Satoshi Yamada, Keisuke Ikari, Masumi Kuwano, Keitaro Murayama, Hirofumi Tomiyama, Suguru Hasuzawa.
Methodology: Satoshi Yamada, Keisuke Ikari, Osamu Togao, Akio Hiwatashi.

Project administration: Tomohiro Nakao, Shigenobu Kanba.

Supervision: Tomohiro Nakao, Shigenobu Kanba.

Writing – original draft: Satoshi Yamada.

Writing – review & editing: Satoshi Yamada.

References
1. Anderson SW, Damasio H, Damasio AR. A neural basis for collecting behaviour in humans. Brain. 2005; 128(Pt 1):201–12. https://doi.org/10.1093/brain/awh329 PMID: 15548551.
2. 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):1038–48. Epub 2004/06/01. https://doi.org/10.1176/appi.ajp.161.6.1038 PMID: 15169692.
3. Mataix-Cols D, Wooderson S, Lawrence N, Brammer MJ, Speckens A, Phillips ML. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch Gen Psychiatry. 2004; 61(6):564–76. Epub 2004/06/09. https://doi.org/10.1001/archpsyc.61.6.564 PMID: 15184236.
4. An SK, Mataix-Cols D, Lawrence NS, Wooderson S, Giampietro V, Speckens A, et al. To discard or not to discard: the neural basis of hoarding symptoms in obsessive-compulsive disorder. Mol Psychiatry. 2009; 14(3):318–31. Epub 2009/04/01. PMID: 19802129.
5. Frost RO, Hartl TL. A cognitive-behavioral model of compulsive hoarding. Behav Res Ther. 1996; 34(4):341–50. Epub 1996/04/01. PMID: 8871366.
6. Mataix-Cols D, Frost RO, Pertusa A, Clark LA, Saxena S, Leckman JF, et al. Hoarding disorder: a new diagnosis for DSM-V? Depress Anxiety. 2010; 27(6):556–72. Epub 2010/03/26. https://doi.org/10.1002/da.20693 PMID: 20336805.
7. Tolin DF, Stevens MC, Villavicencio AL, Norberg MM, Calhoun VD, Frost RO, et al. Neural mechanisms of decision making in hoarding disorder. Arch Gen Psychiatry. 2012; 69(8):832–41. Epub 2012/08/08. https://doi.org/10.1001/archgenpsychiatry.2011.1980 PMID: 22868937; PubMed Central PMCID: PMCPMC3506167.
8. Valente AA Jr., Miguel EC, Castro CC, Amaro E Jr., Duran FL, Buchpiguel CA, et al. Regional gray matter abnormalities in obsessive-compulsive disorder: a voxel-based morphometry study. Biol Psychiatry. 2005; 58(6):479–87. https://doi.org/10.1016/j.biopsych.2005.04.021 PMID: 15978549.
9. Gilbert AR, Keshavan MS, Diwadkar V, Nutche J, Macmaster F, Easter PC, et al. Gray matter differences between pediatric obsessive-compulsive disorder patients and high-risk siblings: a preliminary voxel-based morphometry study. Neurosci Lett. 2008; 435(1):45–50. https://doi.org/10.1016/j.neulet.2007.12.011 PMID: 18314272; PubMed Central PMCID: PMCPMC2365512.
10. Alvarenga PG, do Rosario MC, Batistuzzo MC, Diniz JB, Shavitt RG, Duran FL, et al. Obsessive-compulsive symptom dimensions correlate to specific gray matter volumes in treatment-naive patients. J Psychiatr Res. 2012; 46(12):1635–42. https://doi.org/10.1016/j.jpsychires.2012.09.002 PMID: 23040160.
11. Hough CM, Luks TL, Lai K, Vigil O, Guillory S, Nongpiur A, et al. Comparison of brain activation patterns during executive function tasks in hoarding disorder and non-hoarding OCD. Psychiatry Res. 2016; 255(50–9. https://doi.org/10.1016/j.psychresns.2016.07.007 PMID: 27522332; PubMed Central PMCID: PMCPMC5014569.
12. Nordsetten AE, Fernandes de la Cruz L, Pertusa A, Reichenberg A, Hatch SL, Mataix-Cols D. The Structured Interview for Hoarding Disorder (SIHD): Development, usage and further validation. Journal of Obsessive-Compulsive and Related Disorders. 2013; 2(3):346–50. https://doi.org/10.1016/j.jocrd.2013.06.003
13. Tsuchiyagaito A, Kuroiya K-i, Igarashi T, Horiuchi S, Ando T, Deng K, et al. A Consideration of Clinical Characteristics of Non-Clinical Hoarding among Japanese Adolescents. Anxiety Disorder Research (in Japanese). 2015; 6(2):72–85.
14. Frost RO, Steketee G, Grisham J. Measurement of compulsive hoarding: saving inventory-revised. Behav Res Ther. 2004; 42(10):1163–82. https://doi.org/10.1016/j.brat.2003.07.006 PMID: 15350856.
15. Frost RO, Steketee G, Tolin DF, Renaud S. Development and Validation of the Clutter Image Rating. Journal of Psychopathology and Behavioral Assessment. 2007; 30(3):193–203. https://doi.org/10.1007/s10862-007-9066-7
16. Nakajima T, Nakamura M, Taga C, Yamagami S, Kirike N, Nagata T, et al. Reliability and validity of the Japanese version of the Yale-Brown Obsessive-Compulsive Scale. Psychiatry Clin Neurosci. 1995; 49(2):121–6. Epub 1995/05/01. PMID: 8726128.

17. Rosario-Campos MC, Miguel EC, Quatrano S, Chacon P, Ferrao Y, Findley D, et al. The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): an instrument for assessing obsessive-compulsive symptom dimensions. Mol Psychiatry. 2006; 11(5):495–504. https://doi.org/10.1038/mp. 4001798 PMID: 16432526.

18. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage. 2003; 19(3):1233–9. https://doi.org/10.1016/s1053-8119(03)00169-1 PMID: 12860848.

19. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscale anatomic parcellation of the MNI MRI single-subject brain. Neuroimage. 2002; 15(1):237–89. https://doi.org/10.1016/0956-5282(00)00050-9 PMID: 11771995.

20. Burgess PW, Veitch E, de Lacy Costello A, Sallice T. The cognitive and neuroanatomical correlates of multitasking. Neuropsychologia. 2000; 38(6):848–63. Epub 2000/02/26. PMID: 10689059.

21. Koecchin E, Hyafil A. Anterior prefrontal function and the limits of human decision-making. Science. 2007; 318(5850):594–8. Epub 2007/10/27. https://doi.org/10.1126/science.1142995 PMID: 17962551.

22. Okuda J, Fujii T, Ohtake H, Tsukiura T, Yamadori A, Frith CD, et al. Differential involvement of regions of rostral prefrontal cortex (Brodmann area 10) in time- and event-based prospective memory. Int J Psychophysi. 2007; 64(3):233–46. https://doi.org/10.1016/j.ijpsycho.2006.09.009 PMID: 17126435.

23. Posner MI, Shese BE, Odludas Y, Tang Y. Analyzing and shaping human attentional networks. Neural Netw. 2006; 19(9):1422–9. https://doi.org/10.1016/j.neunet.2006.08.004 PMID: 17059879.

24. Fletcher PC, Henson RN. Frontal lobes and human memory: insights from functional neuroimaging. Brain. 2001; 124(Pt 5):849–81. Epub 2001/05/04. PMID: 11335690.

25. Fleming SM, Weil RS, Nagy Z, Dolen RJ, Rees G. Relating introspective accuracy to individual differences in brain structure. Science. 2010; 329(5998):1541–3. Epub 2010/09/18. https://doi.org/10.1126/science.1191883 PMID: 20847276; PubMed Central PMCID: PPMC3173849.

26. Schmitz TW, Rowley HA, Kawahara TN, Johnson SC. Neural correlates of self-evaluative accuracy after traumatic brain injury. Neuropsychologia. 2006; 44(5):762–73. Epub 2005/09/13. https://doi.org/10.1016/j.neuropsychologia.2005.07.012 PMID: 16154166.

27. de Wit SJ, Alonso P, Schweren L, Mataix-Cols D, Lochner C, Menchon JM, et al. Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. Am J Psychiatry. 2014; 171(3):340–9. Epub 2013/11/14. https://doi.org/10.1176/appi.ajp.2013.13040574 PMID: 24220667.

28. Kim JJ, Lee MC, Kim J, Kim IY, Kim SI, Han MH, et al. Grey matter abnormalities in obsessive-compulsive disorder—Statistical parametric mapping of segmented magnetic resonance images. Brit J Psychiat. 2001; 179:330–4. https://doi.org/10.1192/bjp.179.4.330 PubMed PMID: WOS:000017811460009. PMID: 11581113.

29. Szeszko PR, Christian C, Macmaster F, Lencz T, Mirza Y, Taormina SP, et al. Gray matter structural alterations in psychotropic drug-naive pediatric obsessive-compulsive disorder: an optimized voxel-based morphometry study. Am J Psychiatry. 2008; 165(10):1299–307. Epub 2008/04/17. https://doi. org/10.1176/appi.ajp.2008.08010633 PMID: 18413702.

30. Pujol J, Soriano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, et al. Mapping structural brain alterations in obsessive-compulsive disorder. Arch Gen Psychiat. 2004; 61(7):720–30. Epub 2004/07/09. https://doi.org/10.1001/archpsyc.61.7.720 PMID: 15237084.

31. Togao O, Yoshiura T, Nakao T, Nabeysama M, Sanematsu H, Nakagawa A, et al. Regional gray and white matter volume abnormalities in obsessive-compulsive disorder: a voxel-based morphometry study. Psychiatry Res. 2010; 184(1):29–37. https://doi.org/10.1016/j.psychres.2010.06.011 PMID: 20833001.

32. Okada K, Nakao T, Sanematsu H, Murayama K, Honda S, Tomita M, et al. Biological heterogeneity of obsessive-compulsive disorder: A voxel-based morphometric study based on dimensional assessment. Psychiatry and Clinical Neurosciences. 2015; 69(7):411–21. https://doi.org/10.1111/pcn.12269 PMID: 25556718.

33. Tolin DF, Witt ST, Stevens MC. Hoarding disorder and obsessive-compulsive disorder show different patterns of neural activity during response inhibition. Psychiatry Res. 2014; 221(2):142–8. https://doi.org/10.1016/j.psychres.2013.11.009 PMID: 24389161; PubMed Central PMCID: PPMC3946244.

34. Yoo SY, Roh MS, Choi JS, Kang DH, Ha TH, Lee JM, et al. Voxel-based morphometry study of gray matter abnormalities in obsessive-compulsive disorder. J Korean Med Sci. 2008; 23(1):24–30. https://doi.org/10.3346/jkms.2008.23.1.24 PMID: 18303194; PubMed Central PMCID: PPMC2526479.
35. van den Heuvel OA, Remijse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB, et al. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. Brain. 2009; 132(Pt 4):853–68. https://doi.org/10.1093/brain/awn267 PMID: 18952675.

36. Hoexter MQ, de Souza Duran FL, D’Alcante CC, Dougherty DD, Shavitt RG, Lopes AC, et al. Gray matter volumes in obsessive-compulsive disorder before and after fluoxetine or cognitive-behavior therapy: a randomized clinical trial. Neuropsychopharmacology. 2012; 37(3):734–45. https://doi.org/10.1038/npp.2011.250 PMID: 22030709; PubMed Central PMCID: PMCPMC3260985.

37. Toln DF, Villavicencio A, Umbach A, Kurtz MM. Neuropsychological functioning in hoarding disorder. Psychiatry Res. 2011; 189(3):413–8. https://doi.org/10.1016/j.psychres.2011.06.022 PMID: 21764138; PubMed Central PMCID: PMCPMC3185111.

38. Hartl TL, Frost RO, Allen GJ, Deckersbach T, Steketee G, Duffany SR, et al. Actual and perceived memory deficits in individuals with compulsive hoarding. Depress Anxiety. 2004; 20(2):59–69. https://doi.org/10.1002/da.20010 PMID: 15390215.

39. Lawrence NS, Wooderson S, Mataix-Cols D, David R, Speckens A, Phillips ML. Decision making and set shifting impairments are associated with distinct symptom dimensions in obsessive-compulsive disorder. Neuropsychology. 2006; 20(4):409–19. Epub 2006/07/19. https://doi.org/10.1037/0894-4105.20.4.409 PMID: 16846259.

40. Grisham JR, Brown TA, Savage CR, Steketee G, Bartow DH. Neuropsychological impairment associated with compulsive hoarding. Behav Res Ther. 2007; 45(7):1471–83. https://doi.org/10.1016/j.brat.2006.12.008 PMID: 17341416.

41. Grisham JR, Norberg MM, Williams AD, Certoma SP, Kadib R. Categorization and cognitive deficits in compulsive hoarding. Behav Res Ther. 2010; 48(9):866–72. https://doi.org/10.1016/j.brat.2010.05.011 PMID: 20542489.

42. Ikari K, Nakao T, Nemoto K, Okada K, Murayama K, Honda S, et al. Morphologic and clinical differences between Early- and Late-onset obsessive-compulsive disorder: Voxel-based Morphometric study. Journal of Obsessive-Compulsive and Related Disorders. 2017; 13:35–41. https://doi.org/10.1016/j.jocrd.2017.02.005

43. Boedhoe PS, Schmaal L, Abe Y, Ameis SH, Arnold PD, Batistuzzo MC, et al. Distinct Subcortical Volume Alterations in Pediatric and Adult OCD: A Worldwide Meta- and Meta-Analysis. Am J Psychiatry. 2017; 174(1):60–9. Epub 2016/09/10. https://doi.org/10.1176/appi.ajp.2016.16020201 PMID: 27609241; PubMed Central PMCID: PMCPMC5344782.

44. Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry. 2011; 68(7):675–90. Epub 2011/07/06. https://doi.org/10.1001/archgenpsychiatry.2011.60 PMID: 21727252.

45. Nakao T, Radua J, Rubia K, Mataix-Cols D. Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry. 2011; 168(11):1154–63. Epub 2011/08/26. https://doi.org/10.1176/appi.ajp.2011.11020281 PMID: 21865529.