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ABSTRACT

Although preliminary neuroimaging research suggests that patients with hoarding disorder (HD) show widespread abnormal task-related activity in the brain, there has been no research on alterations in the white matter tracts in these patients. The aim of this study was to investigate the characteristics of the major white matter tracts in patients with HD. Tract-based spatial statistics were used to search for white matter tract abnormalities throughout the brain in 25 patients with HD and 36 healthy controls. Post hoc analysis of regions of interest was performed to detect correlations with clinical features. Compared with the controls, patients with HD showed decreased fractional anisotropy and increased radial diffusivity in anatomically widespread white matter tracts. Post hoc analysis of regions of interest revealed a significant negative correlation between the severity of hoarding symptoms and fractional anisotropy in the left anterior limb of the internal capsule and a positive correlation between the severity of these symptoms and radial diffusivity in the right anterior thalamic radiation. Patients with HD showed a broad range of alterations in the frontal white matter tracts, including the frontothalamic circuit, frontoparietal network, and frontolimbic pathway. The findings of this study indicate associations between frontal white matter abnormalities related to the severity of hoarding symptoms in HD and the cortical regions involved in cognitive dysfunction. The insights provided would be useful for understanding the neurobiological basis of HD.

1. Introduction

Hoarding is a symptom that had been recognized as a subtype of obsessive-compulsive disorder (OCD) until publication of the DSM-5 (Nakao and Kanba, 2019). Hoarding disorder (HD) is included as an obsessive-compulsive related disorder in the DSM-5 and defined as persistent difficulty discarding possessions regardless of their actual value, resulting in accumulation of possessions and cluttered living areas (APA, 2013). Although there are no clear neurobiological models of HD, several neuroimaging studies have found differences in specific brain regions between patients with HD and healthy controls HCs. Functional magnetic resonance imaging (fMRI) has shown that patients with HD have abnormal activation in the left dorsolateral prefrontal cortex (dlPFC) and frontal pole cortex (FPC) and right precentral gyrus during the go/no go task (Tolin et al., 2014); furthermore, Hough et al. found these patients showed greater activation in the bilateral orbitofrontal cortex (OFC), right ventrolateral prefrontal cortex (vlPFC), anterior cingulate cortex, and mid-posterior corpus callosum (Hough et al., 2016). During the stop-signal and switch-signal tasks, patients with HD showed greater activation in the right OFC during successful response switching and less activation in the right dlPFC, OFC, precentral gyrus, and bilateral dorsomedial prefrontal cortex during error processing (Sunol et al., 2020). Moreover, Levy et al. found that their study participants with HD had abnormal functional activation in the bilateral dlPFC, OFC, FPC, medial and lateral temporal cortices, and amygdala during discarding decisions that provoked subjective distress (Levy

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et al., 2021). Using resting state fMRI, they demonstrated that subjects with HD had less functional connectivity in the left orbital and rectal gyri, amygdala, thalamus, and insula in comparison with non-hoarders but greater functional connectivity in the bilateral superior and middle frontal gyri and precuneus (Levy et al., 2019). Previous studies using structural MRI and voxel-based morphometry revealed that patients with HD had a larger volume of gray matter in the right OFC and FPC (Yamada et al., 2018). Several early studies found that OCD patients with hoarding symptoms had abnormal glucose metabolism in the right posterior cingulate gyrus and bilateral dlPFC (Saxena et al., 2004) and greater hemodynamic activation in the left precentral gyrus and right OFC (Mataix-Cols et al., 2004) and in the ventromedial prefrontal cortex bilaterally (An et al., 2009) during tasks that provoke symptoms. Although it is known that the functions of the cortical region are prescribed by its intrinsic properties and extrinsic connections (Passingham et al., 2002), there are no reports on alterations in the white matter (WM) tracts in patients with HD. In contrast, OCD patients with hoarding symptoms have been shown to have a significantly lower WM volume in the left angular gyrus (Hirose et al., 2017) and to demonstrate a negative correlation between severity of hoarding symptoms and axial diffusivity in the right insular gyrus (Yagi et al., 2017). Moreover, there is limited information on the WM tracts in patients with OCD with hoarding symptoms. Therefore, it is still unclear whether or not there are any abnormalities in the WM tracts in patients with HD.

Diffusion tensor imaging (DTI) is a neuroimaging technique that is used to assess the microstructure of WM. Fractional anisotropy (FA) is the DTI parameter most commonly used to assess the degree of diffusion anisotropy and reflects the degree of myelination and fiber crossing, the number of axons and their size, and the properties of the cell membrane; therefore, it has been used as an index of the overall integrity of WM (Roberts et al., 2013). Axial diffusivity (AD) and radial diffusivity (RD) are scalar indices in DTI that are often investigated to gain a deeper understanding of the characteristics of WM. AD reflects diffusivity parallel to axonal fibers whereas RD reflects diffusivity perpendicular to these fibers. Thus, it is thought that AD reflects axonal injury and that RD reflects abnormalities in myelin (Mori and Zhang, 2009). Tract-based spatial statistics (TBSS) are typically used for whole-brain voxel-wise analysis of DTI measures (i.e., FA, AD, and RD) (Smith et al., 2006).

Preliminary neuroimaging findings have been inconsistent, and there are no animal models of HD (Andrews-McClymont et al., 2013); therefore, little is known about the microstructure of WM in the brains of patients with HD. The purpose of this study was to investigate microstructural alterations in the WM tracts of individuals with HD. Using TBSS, we examined FA, RD, and AD to explore abnormalities in the WM tracts throughout the brain, and then performed a post hoc analysis of regions of interest to examine correlations between the microstructural abnormalities identified in WM and clinical characteristics. We anticipated that our findings could contribute to a better understanding of alterations in the WM tracts throughout the brain in patients with HD diagnosed by the DSM-5 and further consideration of previous findings.

2. Material and methods

2.1. Subjects

Sixty-six individuals were recruited for this study, five of whom did not meet the inclusion criteria. Finally, the study included 61 participants, consisting of 25 patients with HD and 36 HCs matched for age, sex, and handedness. The patients with HD were recruited from the outpatient clinic in the Department of Neuropsychiatry, Kyushu University Hospital, Japan, and were registered between November 2014 and June 2020. All were diagnosed by trained psychiatrists to have HD and comorbid disorders using the Structured Interview for Hoarding Disorder (Nordsletten et al., 2013), Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (First, 1997), and Conners' Adult ADHD Diagnostic Interview for DSM-IV (Epstein and Kollins, 2006). We confirmed that hoarding symptoms were not directly associated with the comorbidities. Severity of hoarding symptoms was assessed using the Hoarding Rating Scale-Interview (HRS-I) (Tolin et al., 2010), Clutter Imaging Rating (CIR) (Frost et al., 2008), and Saving Inventory-Revised (SI-R) (Frost et al., 2004). The Hamilton Rating Scale for Anxiety (HAM-A) and Depression (HAM-D: 17-item version) was used to quantify the severity of anxiety and depression (Hamilton, 1959, 1960). The global severity of symptoms of attention deficit hyperactivity disorder (ADHD) was assessed using the Conners' Adult ADHD Rating Scales-Self-Report: Long Version (CAARS-S:L) (Conners et al., 1999) and the Adult ADHD Self-Report Scale-V1.1 Symptoms Checklist (ASRS) (Kessler et al., 2005). Autistic traits were assessed using the Autism-Spectrum Quotient (Baron-Cohen et al., 2001).

HCs were recruited from the local community and interviewed using the Structured Clinical Interview for DSM-IV Non-Patient Edition, HAM-A, and HAM-D (17-item version) by experienced psychiatrists. None of the HCs had ever experienced an Axis I disorder or been prescribed psychiatric medication.

Exclusion criteria for both patients with HD and the HCs were being under the age of 16 years or older than 65 years, a history of psychotic disorder, bipolar disorder, substance abuse, significant head injury, stroke, tumor, or seizure disorder, any severe organic or neurological findings, and clinical evidence of intellectual disability. Based on these criteria, five participants were excluded because of a comorbid diagnosis (schizophrenia, $n = 1$; psychotic disorder due to a general medical condition, $n = 1$; bipolar I disorder, $n = 1$; bipolar II disorder, $n = 2$). The study was approved by the Kyushu University Ethics Committee. All study participants provided written informed consent after receiving a detailed description of the study.

Group differences in the demographic and psychometric data were compared using independent-samples *t*-tests and chi-squared tests. All statistical analyses were performed using IBM SPSS Statistics version 27.0.1 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

2.2. MRI acquisition

All study participants underwent MRI in a 3.0-T MRI scanner equipped with an 8-channel head coil (Achieva TX, Phillips Healthcare, Best, The Netherlands). A DTI scan was acquired using the following scan parameters: repetition time (TR), 7269 ms; echo time (TE), 78 ms; field of view, 230 × 230 mm; matrix, 128 × 128; slice thickness, 2 mm; number of slices, 64; b values: 800 s/mmˆ2, number of motion-probing gradient directions, 32; scan duration, 5 min 28 s. All MRI data were reviewed by an experienced radiologist to exclude clinical abnormalities.

2.3. DTI pre-processing and TBSS analysis

We used the Functional MRI of the Brain (FMRIB) Software Library (FSL) version 5.0.11 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) with Ubuntu version 18.04.1 LTS to analyze the DTI data. Subject movement and eddy current-induced distortions were corrected using Eddy in the FSL (Andersson and Sotiropoulos, 2016). A brain mask that deleted non-brain tissue was created using the Brain Extraction Tool in FSL (Smith, 2002). We used DTIFIT in FSL to fit the diffusion tensor model to each voxel, and then calculated and acquired voxel-wise FA, AD, and RD maps. All FA maps were aligned to a $1 \times 1 \times 1$ mm^3 FMRIB58_FA standard space utilizing the FMRIB nonlinear image registration tool in the FSL. A mean FA map was constructed by averaging the FA maps and then skeletonizing them to create an FA skeleton with a threshold of 0.2. The AD and RD maps were obtained by continually commanding tbss_non_FA in the FSL. These maps were nonlinearly registered, warped, and skeletonized, as for the FA maps. Voxel-wise analysis was then performed based on a general linear model using Randomise in the FSL

with 10000 permutations as recommended for FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/Theory). Age, sex, and handedness were treated as nuisance covariates. The statistical significance threshold was set at $p < 0.05$ for family-wise error correction. All TBSS results included threshold-free cluster enhancement. Significant fiber tracts were identified in the Johns Hopkins University ICBM-DTI-81 White Matter Labels and Johns Hopkins University White Matter Tractography atlases.

2.4. Post hoc analysis of regions of interest

We calculated the mean FA and RD per cluster for each subject using the FSL program implemented in the FSL. Values are reported as the mean and standard deviation. The statistical analysis was performed using the JMP Pro Statistical Software Package (version 14.2.0; SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $p < 0.05$ for false discovery rate correction. First, we performed analysis of covariance (ANCOVA) to assess the main effects of diagnostic group on the mean FA and RD. Age, sex, and handedness were treated as nuisance covariates in ANCOVA. Second, we performed correlation analysis between the demographic and psychometric data (HRS-I, SI-R Total, SI-R Discarding, SI-R Clutter, SI-R Acquiring, CIR mean, HAM-A, HAM-D, ASRS, CAARS-S:L, Autism-Spectrum Quotient) and the FA and RD.

3. Results

3.1. Demographic and psychometric data

The characteristics of the HD and HC groups are shown in Table 1. Both groups were matched for age, sex, and handedness. The HD group had significantly higher anxiety (HAM-A; $p < 0.001$) and depression (HAM-D; $p < 0.001$) scores than the HCs. Fifteen of the 25 patients with HD were medication-free and the remaining 10 were receiving antidepressants (n = 9), major tranquilizers (n = 3), and non-stimulant ADHD agents (n = 3). Seven participants in the HD group were diagnosed with HD only; the remaining 18 participants were concurrently diagnosed with OCD (n = 7), major depressive disorder (n = 4), anxiety disorder (including social anxiety disorder, n = 3; generalized anxiety disorder, n = 2; specific phobia, n = 3; panic disorder, n = 2), posttraumatic stress disorder (n = 3), or ADHD (n = 11) (Table 1).

Table 1
Participant demographic and clinical characteristics.

	HD (N = 25)	HCs (N = 36)	*p* value
Age (years)	43.28 ± 12.21	42.72 ± 10.63	0.18
Female	16 (64%)	23 (63.9%)	>0.99[a]
Right Handedness	24 (96%)	35 (97.2%)	>0.99[a]
HRS-I	28.32 ± 7.41	–	–
SI-R Total	64.36 ± 13.19	–	–
SI-R Discarding	20.96 ± 4.34	–	–
SI-R Clutter	28.20 ± 6.28	–	–
SI-R Acquiring	15.2 ± 5.87	–	–
CIR, mean	4.67 ± 1.97	–	–
HAM-A	6.2 ± 8.2	0.2 ± 0.6	<0.001
HAM-D	6.08 ± 7.04	0.30 ± 0.78	<0.001
ASRS	3.44 ± 1.42	–	–
CAARS-S:L	15.56 ± 5.12	–	–
AQ	27.68 ± 8.51	–	–
Comorbidity			
OCD	7 (28%)	–	–
MDD	4 (16%)	–	–
SAD	3 (12%)	–	–
GAD	2 (8%)	–	–
Specific phobia	3 (12%)	–	–
Panic disorder	2 (8%)	–	–
PTSD	3 (12%)	–	–
ADHD	11 (44%)	–	–
Medication			
Medication-free	15 (60%)	–	–
Antidepressants	9 (36%)	–	–
Major tranquilizers	3 (12%)	–	–
Nonstimulant ADHD drugs	3 (12%)	–	–
Non-GABA hypnotic drugs	2 (8%)		
Benzodiazepines	7 (28%)		
Mood stabilizers	2 (8%)	–	–

Values are mean ± SD or n (%). Percentages represent the proportion of patients within each subgroup.
Abbreviations: HD, hoarding disorder; HCs, healthy controls; HRS-I, Hoarding Rating Scale-Interview; SI-R, Saving Inventory-Revised; CIR, Clutter Imaging Rating; HAM-A, The Hamilton Rating Scale for Anxiety; HAM-D, The Hamilton Rating Scale for Depression; ADHD, attention-deficit hyperactivity disorder; ASRS, Adult ADHD Self-Report Scale-V1.1 Symptoms Checklist; CAARS-S:L, Conners' Adult ADHD Rating Scales-self-Report: Long version; AQ, Autism-Spectrum Quotient; OCD, Obsessive-compulsive disorder; MDD, Major depressive disorder; SAD, Social anxiety disorder; GAD, Generalized anxiety disorder; PTSD, Posttraumatic stress disorder; GABA, Gamma amino butyric acid.
[a] $\chi 2$ test.

3.2. Results from TBSS analysis

The decreased FA areas included the left superior longitudinal fasciculus (SLF), left uncinate fasciculus (UF), left inferior fronto-occipital fasciculus (IFOF), left anterior thalamic radiation (ATR), left corticospinal tract, left anterior limb of the internal capsule (ALIC), left external capsule (EC), left anterior corona radiata (ACR), left superior corona radiata (SCR), left posterior corona radiata (PCR), body of the corpus callosum (CC), and forceps minor (Fig. 1). The RD in patients with HD was increased in the bilateral SLF, right IFOF, bilateral ACR, bilateral SCR, left PCR, right ATR, left posterior thalamic radiation, right EC, right ALIC, CC (genu, body, and splenium), and forceps minor (Fig. 2).

There were no areas with increased FA, decreased RD, or increased or decreased AD in the HD group.

3.3. Results of post hoc analysis of regions of interest

Compared with HCs, the mean FA per cluster was lower in the left SLF ($p = 0.0188$), left EC ($p < 0.0001$), left ALIC ($p = 0.0024$), left UF ($p = 0.0240$), and forceps minor ($p = 0.0481$), and the mean RD per cluster was increased in the right ATR ($p = 0.0253$), right ACR ($p = 0.0190$), left SCR ($p = 0.0492$), and left EC ($p = 0.0120$).

Significant correlations were found between the FA in the left ALIC and SI-R total scores ($r = -0.4404$, $p = 0.0276$), between the RD in the right ATR and HRS-I scores ($r = 0.4507$, $p = 0.0238$), and between the RD in the right ATR and SI-R clutter scores ($r = 0.4312$, $p = 0.0314$) (Fig. 3, Supplemental Table 1).

4. Discussion

In this exploratory TBSS study, we found anatomically widespread decreases in FA and increases in RD in many major WM tracts and correlations between the severity of hoarding symptoms and DTI parameters (FA and RD) in the left ALIC and right ATR, which is part of the frontothalamic circuit. These findings suggest that patients with HD have microstructural alterations in the prefrontal WM tracts. To our knowledge, this is the first study to find major abnormalities in the WM tracts within the brain and correlations between DTI indices and clinical features in patients with HD.

We found decreased FA in the left ALIC and increased RD in the right ATR in our HD group. Moreover, we found a negative correlation between SI-R total scores and FA in the left ALIC, a positive correlation between HRS-I scores and RD in the right ATR, and a positive correlation between SI-R clutter scores and RD in the right ATR in the HD group. The ATR is a corticothalamic and thalamocortical projection fiber bundle that connects the medial thalamic nuclei to the dlPFC, vlPFC, and OFC bilaterally via the ALIC and ACR (Jang and Yeo, 2014). Previous MRI studies have shown evidence of abnormal neural activity and volumetric changes in the dlPFC, vlPFC, OFC, and thalamus in patients with HD (An

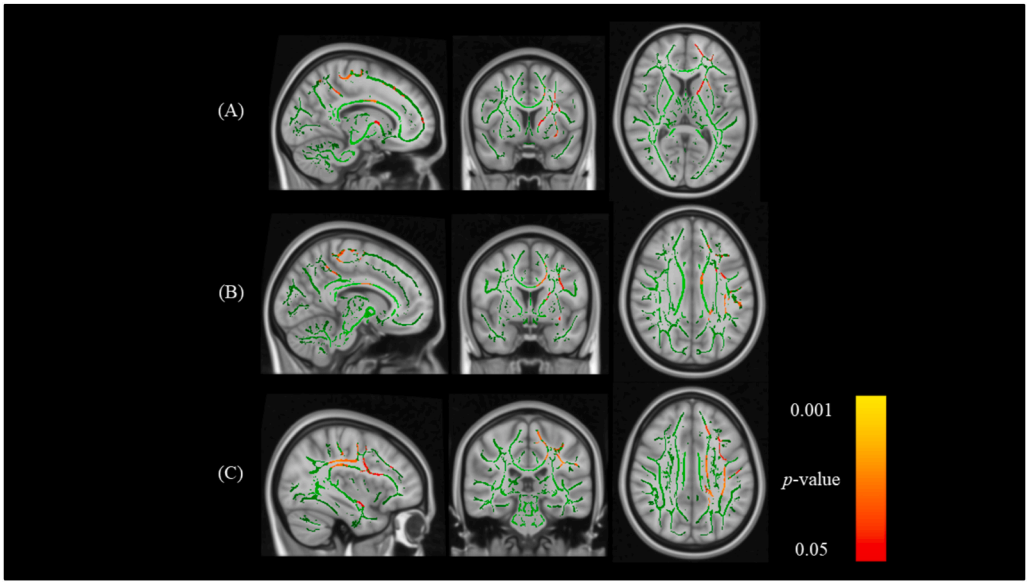

Fig. 1. Group differences in decreased FA.
Group differences in fractional anisotropy (FA) between patients with hoarding disorder (HD) and healthy controls (HCs). White matter (WM) tracts showed significantly decreased FA [$p < 0.05$, threshold-free cluster enhancement (TFCE) corrected for multiple comparisons] in **(A)** the left anterior thalamic radiation (ATR), left anterior limb of internal capsule (ALIC), left external capsule (EC), left uncinate fasciculus (UF), left inferior fronto-occipital fasciculus (IFOF), and forceps minor, **(B)** body of corpus callosum (CC), and **(C)** left superior longitudinal fasciculus (SLF), left anterior corona radiata (ACR), left superior corona radiata (SCR), left posterior corona radiata (PCR), and left corticospinal tract.

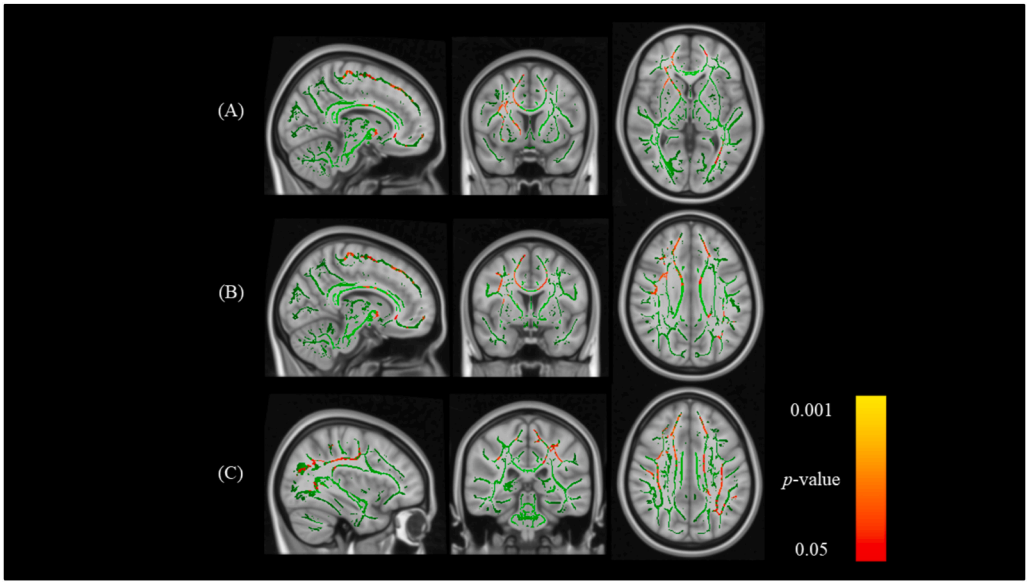

Fig. 2. Group differences in increased RD.
Group differences in radial diffusivity (RD) between patients with hoarding disorder and healthy controls. White matter (WM) tracts showed significantly increased RD [$p < 0.05$, threshold-free cluster enhancement (TFCE) corrected for multiple comparisons] in **(A)** right anterior thalamic radiation (ATR), right anterior limb of internal capsule (ALIC), right external capsule (EC), right inferior fronto-occipital fasciculus (IFOF), left posterior thalamic radiation, and forceps minor, **(B)** corpus callosum (genu, body, and splenium), and **(C)** bilateral superior longitudinal fasciculus (SLF), bilateral anterior corona radiata (ACR), bilateral superior corona radiata (SCR), and left posterior corona radiata (PCR).

et al., 2009; Hough et al., 2016; Levy et al., 2019, 2021; Sunol et al., 2020; Tolin et al., 2009, 2014; Yamada et al., 2018). Patients with HD were found to have both WM tract alterations in the ATR and ALIC in the current study and abnormal neural activity in the PFC and thalamus according to preliminary research, which are anatomically connected by the ATR; therefore, patients with HD may have dysfunction in the frontothalamic circuit, which is thought to play an important role in executive functions, including working memory (Mamah et al., 2010), attention (Jagtap and Diwadkar, 2016), reward processing (Coenen et al., 2012), and decision-making (Sieveritz et al., 2019). Several studies have reported that frontothalamic circuit-related cognitive functions (executive functions including memory, attention, reward processing, and decision-making) are impaired in patients with HD and suggest that these impairments underlie hoarding symptoms such as acquiring, saving, and cluttering relevant to HD (Ayers et al., 2013; McMillan et al., 2013; Tolin et al., 2011; Wheaton and Topilow, 2020). While previous fMRI studies using hoarding symptom provocation tasks showed that abnormal neural activity in the cingulo-opercular network is associated with symptoms of HD (Stevens et al., 2020; Tolin et al., 2012), no study has demonstrated neural abnormalities in the frontothalamic circuit that are associated with the severity of hoarding symptoms. Our findings of abnormal FA and RD in the ATR and ALIC in patients with HD reflect the abnormalities in WM in the frontothalamic circuit, and these alterations were related to the severity of hoarding symptoms. It is noteworthy that, in addition to the cingulo-opercular network, alterations in the WM tract within the frontothalamic circuit are associated with the severity of symptoms of HD. In this study, we showed anatomically widespread alterations in several major WM tracts that connect the brain regions involved in homologous cognitive function. Moreover, our study reveals an association of WM tract abnormalities related to severity of hoarding symptoms with the connected cortical regions involved in cognitive dysfunction in HD.

Using TBSS and post hoc analysis of regions of interest, we found decreased FA in the left SLF in patients with HD. The SLF is the largest bundle of association fibers and is composed of three distinct branches. Thiebaut de Schotten et al. contended that “In humans, the first branch

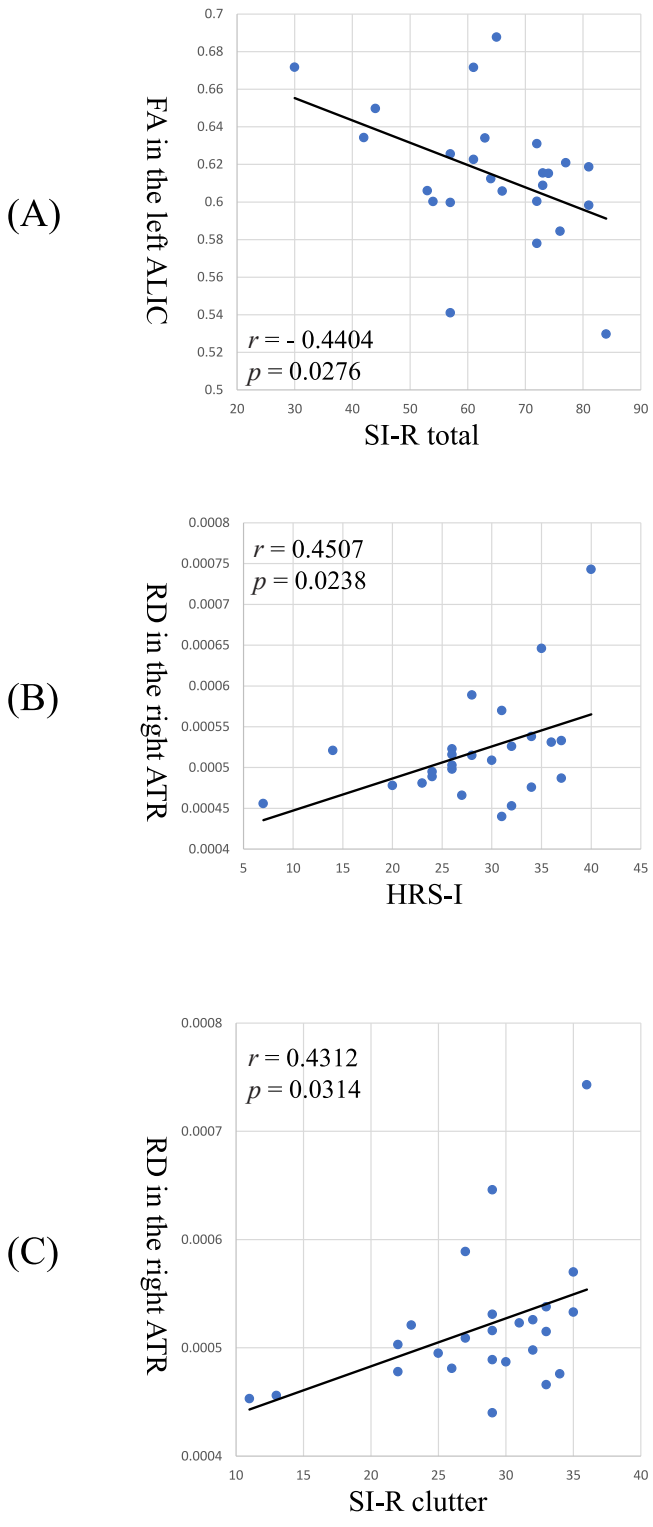

Fig. 3. Significant correlations between severity of hoarding symptoms and FA and RD.

Shown are **(A)** negative correlations between Saving Inventory-Revised (SI-R) total scores and fractional anisotropy (FA) in the left anterior limb of the internal capsule (ALIC) and positive correlations **(B)** between Hoarding Rating Scale-Interview (HRS-I) scores and radial diffusivity (RD) in the right anterior thalamic radiation (ATR) and **(C)** between SI-R clutter scores and RD in the right ATR.

of the superior longitudinal fasciculus (SLF I) connects to the superior parietal lobule and precuneus (BA 5 and 7), to the superior frontal (BA 8, 9, 32), and perhaps to some anterior cingulate areas (BA 24). The second branch (SLF II) originates in the anterior intraparietal sulcus and the angular gyrus (BA 39 and 40) and terminates in the posterior regions of the superior and middle frontal gyrus (BA 6, 8, 9). The third branch (SLF III) connects the intraparietal sulcus and inferior parietal lobule to the inferior frontal gyrus (BA 44, 45, 47)" (Thiebaut de Schotten et al., 2012). Previous MRI studies indicated that patients with HD showed different task-related or resting-state activation in these brain regions, including the precuneus and superior, middle, and inferior frontal gyri, which are connected by the SLF (Hough et al., 2016; Levy et al., 2019, 2021; Stevens et al., 2020; Sunol et al., 2020; Tolin et al., 2009, 2014). The SLF contributes to a broad range of cognitive functions, including visuospatial processing, attention, and working memory (Nakajima et al., 2020). Furthermore, the SLF is a major WM tract in the fronto-parietal network (Thiebaut de Schotten et al., 2011), which plays an important role in executive functions, such as initiating attentional control and adjusting top-down control (Dosenbach et al., 2008). Several studies have reported that individuals with HD performed worse on cognitive tasks involving visuospatial processes, attention, and working memory (Mackin et al., 2016; McMillan et al., 2013). A resting-state fMRI study also showed abnormal functional connectivity in the frontoparietal network in patients with HD (Levy et al., 2019). Therefore, decreased FA in the left SLF reflects alterations in WM in the frontoparietal network in these patients and may be associated with cognitive impairments, such as task-switching and inhibition, as shown in previous studies (Hough et al., 2016; Sunol et al., 2020).

In the present study, we also found decreased FA in the left UF and EC and increased RD in the left UF. The UF is an association fiber bundle that reciprocally connects the OFC and FPC to the anterior temporal lobes (temporal pole, uncus, parahippocampal gyrus, and amygdala) via the EC (Catani et al., 2002; Von Der Heide et al., 2013). Several neuroimaging studies have found that individuals with HD show abnormal functional connectivity in the left orbital gyrus, parahippocampal gyrus, and amygdala (Levy et al., 2019) and abnormal task-induced activity in the left FPC, OFC, superior temporal gyrus, and amygdala (An et al., 2009; Hough et al., 2016; Levy et al., 2021; Tolin et al., 2009, 2014). The UF, variously called 'the frontotemporal circuit' (Ramnani et al., 2004), 'temporo-amygdala-orbitofrontal network' (Catani et al., 2013), or 'frontolimbic pathway' (Tromp et al., 2012), plays an important role in emotional regulation, episodic memory, object-reward association learning, and reversal learning (Von Der Heide et al., 2013). Many studies have shown that these cognitive domains are also impaired in patients with HD (Hartl et al., 2004; Morein-Zamir et al., 2014) and that their difficulties of self-reported emotional regulation are positively correlated with the severity of hoarding symptoms (Taylor et al., 2018; Tolin et al., 2018). Recent fMRI research revealed that sadness, regret, and sentimental attachment during symptom-provocation decision-making tasks are associated with neural activity in the amygdala, OFC, FPC, and medial and lateral temporal lobes (Levy et al., 2021). These findings suggest that part of the pathophysiology of HD lies in the frontolimbic pathway. In summary, abnormal diffusion parameters in the UF and EC indicate abnormalities in WM in the frontolimbic pathway in HD and may be associated with hoarding-related emotional processing (Levy et al., 2021).

The DTI-derived measure of FA has been previously recognized as an indicator of the integrity of WM (Jones et al., 2013). Although this interpretation is correct in some situations, such as the development of the human brain (Lebel and Beaulieu, 2011), recent research using diffusion MRI with microscopy revealed that FA was sensitive to myelination (Chang et al., 2017). In addition, earlier studies showed that RD may reflect myelin damage in mouse models of WM abnormalities (Song et al., 2002, 2003, 2005); thus, RD has been recognized overall as a pathology involving myelin. Use of a combination of diffusion MRI and microscopy in a mouse model showed that RD was sensitive to

myelination in a limited number of WM tracts (Chang et al., 2017). It is known that myelination and oligodendrocyte in the WM play an important role in pathophysiology of psychiatric disorders (Nave and Ehrenreich, 2014), and moreover alteration in myelination affect neural circuit dynamics and, consequently, cognitive function (see review (Monje, 2018)). Given that the changes of FA and RD indicate myelin pathology, our findings suggest that the pathophysiology of HD may include abnormalities of myelination; moreover, the changes in myelination that we have identified may underlie previous findings showing correlation between the severity of hoarding symptoms and cognitive impairment (Ayers et al., 2013; Taylor et al., 2018; Tolin et al., 2018; Wheaton and Topilow, 2020).

This study has several limitations. First, our sample size was relatively small to perform a robust DTI analysis. Second, 40 percent of the participants in the HD group were on psychiatric medication at the time of the study. Finally, a number of patients with HD had comorbid psychiatric disorders, including ADHD, OCD, major depressive disorder, anxiety disorder, and posttraumatic stress disorder. There is adequate evidence from TBSS studies that patients with these psychiatric conditions also have microstructural abnormalities in WM (Aoki et al., 2018; Jenkins et al., 2016; Piras et al., 2021; Siehl et al., 2018; Wise et al., 2016). In particular, the participants in the HD group had a higher rate of comorbid ADHD (44%) than in previous studies (16.7–27.8%) (Frost et al., 2011; Kuwano et al., 2020; Levy et al., 2021; Stevens et al., 2020). This difference might reflect a degree of sampling bias arising from the small sample size. In a recent meta-analysis of TBSS studies, patients with ADHD showed decreased FA in the CC, bilateral IFOF, left inferior longitudinal fasciculus, and right SLF (Aoki et al., 2018), which is partly overlapped with our present results. Furthermore, several studies have reported that impairments in executive function are common to both HD and ADHD (Pievsky and McGrath, 2018; Woody et al., 2014). This finding suggests that HD and ADHD share a common pathophysiology. Although these comorbidities would undoubtedly have affected the findings of the present study, we found no significant correlations between the clinical characteristics of patients with HD and the FA or RD; therefore, our findings could reflect microstructural abnormalities in WM not found in psychiatric comorbidities but rather in HD. Despite these limitations, this study contributes to our understanding of alterations in the WM tracts of the brain in HD (as defined by the DSM-5 criteria). Further studies that include larger sample sizes, non-medicated subjects, controls for comorbidities and medications, and structured interviews to assess HD and psychiatric comorbidities are needed to clarify the features of the WM tracts in the brain in patients with HD.

5. Conclusion

This study found anatomically widespread abnormal FA and RD in many major WM tracts, including the frontothalamic circuit, frontoparietal network, and frontolimbic pathway. We also found significant correlations between the severity of hoarding symptoms and DTI parameters in the frontothalamic circuit. The finding of a characteristic association between alterations in the prefrontal WM tract, which connects cortical regions involved in cognitive function, and the severity of hoarding symptoms could provide new insights into the neurobiological basis of HD. Additional studies that include cognitive assessment and consideration of comorbidities are needed to elucidate the pathophysiology of HD.

Contributors

Taro Mizobe: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Project administration. **Keisuke Ikari**: Validation, Formal analysis, Writing - Review & Editing. **Hirofumi Tomiyama**: Investigation, Writing - Review & Editing. **Keitaro Murayama**: Investigation, Writing - Review & Editing. **Kenta Kato**: Investigation. **Suguru Hasuzawa**: Investigation. **Osamu Togao**: Data Curation. **Akio Hiwatashi**: Data Curation. **Tomohiro Nakao**: Supervision, Writing - Review & Editing, Funding acquisition.

All authors approved the final version of the manuscript.

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No funding sources had involved in the current study.

Declaration of competing interest

Declarations of interest: none.

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Appendix A. Supplementary data

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