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Compromised Cerebello-Thalamic White Matter Integrity in Medication-Free Patients with Obsessive-Compulsive Disorder

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Compromised Cerebello-Thalamic White Matter Integrity in Medication-Free Patients with Obsessive-Compulsive Disorder

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Abstract

The cerebello-thalamic tract is the only efferent white matter (WM) bundle of the cerebellum that connects the cerebellum to the thalamus and has recently attracted much attention in obsessive-compulsive disorder (OCD) with its integral role in higher order cognitive functions commonly known to be impaired in OCD patients. Previous neuroimaging studies have shown that the cerebello-thalamic connection is functionally impaired in OCD patients, and that functional abnormalities in the cerebello-thalamic circuit has correlates with OCD symptom severity scores, highlighting the dysconnectivity between the cerebellum and the thalamus is associated with OCD pathophysiology. However, the WM integrity of the cerebello-thalamic tract in OCD, which may underly functional abnormalities of the cerebello-thalamic connection, is not yet sufficiently understood. Therefore, the current study aimed to elucidate whether compromised cerebello-thalamic WM integrity is observed in medication-free OCD patients. This study included 106 medication-free OCD patients and 105 matched healthy controls (HCs). T1-weighted imaging and diffusion tensor imaging was acquired from every participant. To reconstruct the bilateral cerebello-thalamic tract with accurate anatomical characteristics, probabilistic tractography was used in this study. Three diffusion indices (fractional anisotropy, FA; mean diffusivity, MD; radial diffusivity, RD) were measured from the reconstructed bilateral cerebello-thalamic tract and then compared between groups. As a result of analysis, patients with OCD showed significantly increased MD and RD in the right cerebello-thalamic tract compared to HCs, and there was no difference in FA between groups. In addition, MD and RD of the right cerebello-thalamic tract of patients with OCD showed significantly lateralized to the right, and there's no structural asymmetry for FA. Overall, this study revealed compromised WM microstructure

of the right cerebello-thalamic tract in patients with OCD, which may indicate the underlying structural abnormalities in the dysfunctional cerebello-thalamic circuit in OCD patients, suggesting that compromised WM microstructure of the right cerebello-thalamic tract may underlie OCD pathophysiology, such as OC-like behavior or cognitive dysfunctions in patients with OCD.

Keyword: Obsessive-compulsive disorder; Cerebello-thalamic tract; White matter; Diffusion tensor imaging; Probabilistic tractography

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1. Introduction

1.1 Characteristics of obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by repetitive and intrusive thoughts, images, impulses or urges (obsession) and maladaptive compulsive behaviors or mental acts (compulsion) that interfere with an individual's life (Robins et al., 1984; Stein, 2002). Major cognitive impairments found in patients with OCD include alterations to visuospatial memory, dysfunctions to executive function, and impairment of verbal memory or verbal fluency (Shin, Lee, Kim, & Kwon, 2014). Since patients with OCD are heterogeneous group, exhibiting various OC symptom dimensions such as aggressive/checking, contamination/cleaning, symmetry/ordering, and sexual/religious, the current symptom-based classification of OCD is difficult to reflect the pathophysiology of OCD (Rosario et al., 2006; van den Heuvel et al., 2009), so biological evidence such as neurocircuitry model should be considered together to diagnose OCD (Lack et al., 2012).

Although the exact pathophysiology of OCD has not yet been clearly identified, the most reported neurocircuitry model in many studies on OCD is the cortico-striato-thalamo-cortical (CSTC) circuitry model, which is composed of the cortex, striatum, and thalamus, and it has been reported that functional or structural abnormalities for CSTC circuitry are associated with major clinical symptoms or cognitive impairments in patients with OCD (Graybiel & Rauch, 2000; J. S. Kwon, Jang, Choi, & Kang, 2009; Milad & Rauch, 2012; Pauls, Abramovitch, Rauch, &

Geller, 2014). However, along with the CSTC circuitry, accumulating evidence has highlighted the cerebello-thalamic circuit, in that they contribute to various cognitive dysfunctions commonly found in OCD patients (De Smet, Paquier, Verhoeven, & Marien, 2013; J. S. Kwon et al., 2009; Stoodley, 2012; Strick, Dum, & Fiez, 2009).

1.2 Characteristics of the cerebello-thalamic tract

Through a study of transneuronal tracing technique using retroviruses on the cerebellum, it was revealed that the cerebellum is known to communicate with various brain areas through two afferent and one efferent white matter (WM) bundles (Bostan, Dum, & Strick, 2013). In particular, the cerebello-thalamic tract is the only efferent WM bundle of the cerebellum, known as a tract that directly connects the cerebellum and the thalamus, and is characterized by anatomical features that the left and right cerebello-thalamic tract intersect at the midbrain area (Mollink et al., 2016; van Baarsen et al., 2016). Conventionally, cerebello-thalamic connection has been considered to mostly involved in motor function such as motor coordination or motor control. However, recently, it has been reported that the cerebello-thalamic connection modulates higher cognitive functions such as visuospatial cognition, executive function, and linguistic processing, which are consistently reported to be altered in patients with OCD (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Eng, Sim, & Chen, 2015; Stoodley & Schmahmann, 2009). For example, Ide and Li reported that the connection between the cerebellum and the thalamus is related to error-related

cognitive control which is an executive function (Ide & Li, 2011), and Ward showed that in the case with infarction to the cerebello-thalamic tract, impulses to compulsive behavior have been observed (Ward, 1988). As such, the cerebello-thalamic tract has recently attracted much attention in OCD in that it is related to cognitive and behavioral dysfunctions commonly found in OCD patients.

1.3 Functional studies on the cerebello-thalamic connection in OCD

Recent functional magnetic resonance imaging (fMRI) studies have reported increased (Li et al., 2019; Lv et al., 2021; Sha et al., 2020) or decreased cerebello-thalamic functional connectivity or network patterns (Hou et al., 2014; Tikoo et al., 2021; Xu et al., 2019) in patients with OCD and some studies have reported a positive or negative correlation with OCD symptom severity score (Sha et al., 2020; Xu et al., 2019). For example, Hou et al., reported that the cerebello-thalamic functional connectivity is increased in OCD patients (Hou et al., 2014), whereas Xu et al., reported that the functional connectivity between the cerebellum and the thalamus were significantly decreased in OCD patients and is positively correlated with OCD symptom severity (Xu et al., 2019). Although the findings are inconsistent among studies, these findings not only confirmed that the cerebello-thalamic connection is functionally altered in patients with OCD, but also highlighted the functional dysconnectivity between the cerebellum and the thalamus on OCD pathophysiology such as OC symptoms or cognitive impairment, suggesting the possibility that the cerebello-thalamic connection may

reflect functional mechanism of the pathophysiology of OCD (Heinzel et al., 2018; Moreira et al., 2019; Niu et al., 2017; Yang et al., 2010). However, the exact pathogenesis is still poorly understood. Therefore, to better comprehend the pathophysiology of OCD, despite functional abnormalities in the cerebello-thalamic circuit in OCD patients, an understanding of the compromised white matter (WM) structural connection between the cerebellum and the thalamus is necessary in that it may underlie the cerebello-thalamic functional dysconnectivity (Greicius, Supekar, Menon, & Dougherty, 2009; Toosy et al., 2004; van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009).

1.4 Diffusion tensor imaging

The most commonly used method for studying WM is diffusion tensor imaging (DTI) technique. The basic principle of DTI is to quantitatively measure the degree of diffusion of water molecules in tract. In gray matter or cerebrospinal fluid, water molecules diffuse equally in all directions, so the shape of the tensor has a spherical, but in contrast, water molecules in WM have anisotropy that spreads better in parallel direction than in the vertical direction of nerve fibers, resulting in a fan-shaped tensor structure (Blain et al., 2006). From these characteristics, DTI parameter, a quantitative indicators of DWI image, can be calculated using eigenvalue. Diffusion index can be largely divided into anisotropic parameter and diffusivity parameter. Fractional anisotropy (FA) is a parameter representing the degree of anisotropy, which indicates the direction of water molecules (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). Since highly anisotropic nerve fibers

increase the efficiency of neural signaling, an increase in FA value is often considered an indicator of the healthy or maturity of white matter (Winston, 2012). In addition to FA, complementary information to infer the characteristics or causes of detailed changes in tract can be obtained through diffusivity parameters. Diffusivity parameters include mean diffusivity (MD) and radial diffusivity (RD). MD is an average of three eigenvectors, which indicates the average water molecule diffusivity in the voxel, and the higher the value, the higher the diffusion rate of water into the extracellular space (Bennett, Madden, Vaidya, Howard, & Howard, 2010). RD is a parameter that quantifies the direction of diffusion perpendicular to the main diffusion direction and is known as an indicator that reflects the myelination state of axon (Song et al., 2003; Song et al., 2002). Previous studies have presented FA and MD values representatively reflecting the integrity of white matter and have additionally presented RD that provides information on the direction of diffusion (Bennett et al., 2010).

Conventionally, aberrant WM fiber shows decreased FA and increased MD and RD. In principle, when the organization of the tract is rigid and uniform and the water diffusion rate is faster along the parallel direction to the axons compared to the perpendicular direction to the tract, the WM structure becomes a fan-shaped, and at this time, the anisotropy and parallel diffusivity are said to be increased (Basser, 1995). On the contrary, at the same condition, water diffusion rate in the direction perpendicular to the tract decreases, thereby reducing perpendicular diffusivity (Song et al., 2003; Song et al., 2002). Thus, considering that anisotropy represents the degree of diffusion in the principal direction

compared to the two orthogonal perpendicular directions, the direction of the relationship between anisotropy and diffusivity perpendicular to the tract is often the opposite in WM fiber (Figley et al., 2021; Winklewski et al., 2018). However, there are several exceptions to this interpretation such as crossing fiber or low signal-to-noise ratio (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Wheeler-Kingshott, Ciccarelli, Schneider, Alexander, & Cercignani, 2012). For example, if the increase in diffusivity due to brain damage or brain disease increases at the same proportion in WM tract, MD and RD increases since net magnitude of diffusivity increases, but the FA is still intact because the principal direction of diffusion is still constant (Figley et al., 2021; Schilling et al., 2017). Therefore, in order to confirm the abnormality of the WM structure, FA, which is a relative measurement, and MD and RD, which are absolute measurements, should be considered together in interpreting the change in diffusion indices.

1.5 DTI studies on the cerebello-thalamic tract in OCD

To date, the majority of previous DTI studies in OCD used hypothesis-free whole-brain comparison analysis (i.e., tract-based spatial statistics [TBSS]) to identify specific regions of WM alterations across the whole brain, and there are two DTI studies reported aberrant integrity in several WM regions in OCD patients including the superior cerebellar peduncle (SCP) (Jayarajan et al., 2012; Tikoo et al., 2021). The SCP is known as the cerebello-thalamic tract, the tract connecting the dentate nucleus, one of the deep cerebellar nuclei, and the thalamus (H. G. Kwon et al., 2011; Mollink et al., 2016; Silk, Chen, Seal, & Vance, 2013).

Jayarajan et al., reported an increased RD in the right cerebello-thalamic tract but no difference in FA and MD in juvenile OCD patients with medication (Jayarajan et al., 2012). On the other hand, Tikoo et al., reported decreased FA and increased MD in the left cerebello-thalamic tract in drug-naïve child OCD patients (Tikoo et al., 2021). Although there are discrepancies between studies, these studies have shown that the WM structure of the cerebello-thalamic tract is impaired in OCD patients. However, those findings may not be sufficient to determine whether the WM integrity of the cerebello-thalamic tract is actually altered in OCD, as those findings are derived from hypothesis-free whole-brain comparison analysis such as TBSS, making it difficult to distinguish between the cerebello-thalamic tract and adjacent WM fibers such as the central tegmental tract or medial longitudinal fasciculus (Kuchling et al., 2018; Preti et al., 2012). In addition, TBSS method is less specific in that in investigates changes in the diffusion index in small areas of the corresponding WM skeleton, which is different from WM tract. Therefore, it is necessary to confirm whether the WM integrity of the cerebello-thalamic tract is actually compromised in OCD by using a method that can investigate the WM integrity of the entire tract reflecting accurate anatomical characteristics.

1.6 Probabilistic tractography method

Tractography can be classified into two classes: deterministic and probabilistic tractography. Since deterministic tractography has difficulty explaining uncertainty in estimates of fiber orientation, probabilistic tractography, which can account this limitation well, is generally considered a better method to reconstruct

and dissect individual WM fibers compared to other method (Sotiropoulos & Zalesky, 2019). Probabilistic tractography method is a fiber-tracking technique that allows specific tracing of anatomical connections between different brain regions depends on the probability density function (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Catani & Thiebaut de Schotten, 2008) and is relatively appropriate for examining the WM integrity of the entire tract because it could reconstruct the fan-shaped WM structure (Kanaan et al., 2006; Mori, Crain, Chacko, & van Zijl, 1999). The Main advantage of using probabilistic tractography is that it covers a larger proportion of the tract of interest than whole-brain comparison analysis (Mukherjee, Berman, Chung, Hess, & Henry, 2008). Furthermore, probabilistic tractography method has another advantage of being able to reconstruct WM tract reflecting accurate anatomical features of the corresponding fiber, even if it is a WM tract with a crossing fiber (van Baarsen et al., 2016). Thus, using probabilistic tractography, structural fingerprints of the cerebello-thalamic tract can be more reliably and reproducibly reconstructed and quantified than existing hypothesis-free whole-brain analysis such as TBSS, in that probabilistic tractography examines changes in the diffusion index of the entire tract rather than measuring regional diffusion index changes, as in hypothesis-free whole-brain analysis (van Baarsen et al., 2016). Despite these advantages, however, there have been no studies to date examining the integrity of the cerebello-thalamic tract in patients with OCD by applying probabilistic tractography.

1.7 Purpose of research

In accordance with the altered cerebello-thalamic circuitry observed in fMRI studies of patients with OCD, this dissertation aimed to elucidate whether aberrant WM integrity of the cerebello-thalamic tract is observed in medication-free OCD patients compared to that of healthy controls (HCs). In addition, in order to solve the limitations of the existing whole brain TBSS approach and confirm the WM integrity of the cerebello-thalamic tract, this study intend to use probabilistic tractography (van Baarsen et al., 2016). Based on findings from previous functional (Chen et al., 2016; Heinzel et al., 2018; Peng et al., 2014; Thorsen et al., 2018; Vaghi et al., 2017) and structural studies in OCD (Jayarajan et al., 2012; Tikoo et al., 2021), this study was hypothesized that the WM integrity of the cerebello-thalamic tract is compromised in medication-free OCD patients compared to HCs. Specifically, as generally observed in aberrant WM fibers, it was expected that decreased FA and increased MD and RD would be observed in the cerebello-thalamic tract of OCD patients in this study.

2. Methods

2.1 Participants

A total of 107 medication-free OCD patients (age range 13 ~ 48 years) and 110 age-, sex-, handedness-, IQ and education years-matched HCs (age range 17 ~ 48 years) participated in this study. OCD patients were recruited from the OCD clinic at Seoul National University Hospital (SNUH), of which 45 patients were drug-naïve, and 62 had been unmedicated for more than four weeks prior to study participation (Berney et al., 2011). Since current study included only medication-free or drug-naïve OCD patients, drug effects were considered to be controlled for, and therefore information about drug use was not included in this paper. Diagnosis of OCD and comorbid psychiatric disorders was assessed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria by certified psychiatrists (Association, 1994). For OCD patients, OC symptom severity and accompanying depression and anxiety symptoms were assessed with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Rating Scale for Depression (HAM-D), and Hamilton Rating Scale for Anxiety (HAM-A), respectively (Goodman et al., 1989; Hamilton, 1959, 1960). HCs were recruited from online advertisements and were screened using the Structural Clinical Interview for DSM-IV Nonpatient Edition (SCID-NP) (Spitzer, Williams, Gibbon, & First, 1992). HCs were excluded when they had any first- to third-degree relatives with psychotic disorders. Exclusion criteria for all subjects were intellectual disability (IQ < 70), history of severe head injury accompanying loss

of consciousness, neurological disorder, substance abuse (except nicotine), and severe medical illness that could affect cognitive functioning.

Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki after they were given a thorough explanation of the study procedure (IRB nos. H-1201-008-392). For those who were less than 18 years old, written informed consent was obtained from both participants and their parents. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of SNUH (IRB no. H-2201-054-1289).

2.2 Image acquisition

All subject data were acquired using a 3T MRI scanner (Magnetom Trio; Siemens, Erlangen, Germany). T1-weighted imaging (T1WI) and diffusion-weighted imaging (DWI) data were acquired. T1WI data were acquired in the sagittal section using a three-dimensional magnetization-prepared rapid acquisition echo (MPRAGE) sequence [voxel size = 1 × 0.98 × 0.98 mm3, repetition time (TR) = 1670 ms, echo time (TE) = 1.89 ms, field of view (FOV) = 250 mm, flip angle = 9°, 208 slices]. DWI images were acquired in the axial section using echo-planar imaging [voxel size = 1.9 × 1.9 × 3.5 mm^3, TR = 11400 ms, TE = 88 ms, matrix = 128 × 128, FOV = 240 mm]. Diffusion-sensitizing gradient echo encoding was applied in 64 gradient directions (b-value = 1000 s/mm^2). Non-DWI (B0) volume was acquired at the beginning of each scan.

2.3 Image processing

T1WI data were preprocessed using FreeSurfer version 7.1.0 to extract brain tissue from the whole head image (https://surfer.nmr.mgh.harvard.edu/). All preprocessing steps were conducted according to the automated FreeSurfer pipeline. Using FLIRT with a mutual information cost function and FNIRT with transformation matrices that were obtained from the linear method, each T1WI data point was registered to the Montreal Neurological Institute (MNI) standard space (2 x 2 x 2 mm^3) (Ashburner & Friston, 1999).

DWI data was preprocessed using the Functional MRI of the Brain (FMRIB) Software Library (FSL version 6.0.5, https://www.fmrib.ox.ac.uk/fsl) to remove nonbrain tissue (Smith, 2002) and correct eddy-current induced distortions as well as head motion (Andersson & Sotiropoulos, 2016). All data was visually inspected for major artifacts. When registering the T1WI data to the diffusion-weighted space, B0 images of each subject were used as references. Initially, affine matrices were created to transform T1WI data to diffusion-weighted space using FLIRT with a mutual information cost function. Then, these metrices were combined with transforms that were previously created from T1WI nonlinear registration to the MNI space (Ashburner & Friston, 1999).

2.4 Probabilistic tractography and diffusion index calculation

To evaluate WM integrity of the cerebello-thalamic tract, FSL probabilistic tractography (Behrens et al., 2007) for each side of the brain with default option of the probtrackx2 GPU (curvature threshold = 78°, streamlines per voxel = 5000,

maximal number of steps = 275, step length = 0.5 mm, loopcheck, one-way condition) was conducted using the ipsilateral dentate nucleus (Hernandez-Fernandez et al., 2019), taken from the Probabilistic Atlas of the Cerebellum (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009) at a 50% threshold, as a seed region (**Figure 1A**), and the contralateral thalamus, taken from the Oxford Thalamic Connectivity Atlas (Behrens et al., 2003) at a 50% threshold, as both target region and waypoint (**Figure 1B**) (van Baarsen et al., 2016). The criterion for determining the left and right cerebello-thalamic tract depends on which side of the dentate nucleus is the seed region. For example, in the case of the left cerebello-thalamic tract, the left dentate nucleus was selected as a seed region, and the right thalamus was selected as an end point. For the cerebello-thalamic tract, to prevent interference with cerebellar regions other than the dentate nucleus, the cerebellar vermis was used as an exclusion mask. In addition, to increase the probability accuracy of the cerebello-thalamic tract, the contralateral thalamus and dentate nucleus were chosen as exclusion masks on each side of the cerebello-thalamic tract. For example, in the case of the left cerebello-thalamic tract, the right dentate nucleus and left thalamus were chosen as exclusion masks.

Then, three diffusion indices (FA, MD, and RD) were extracted from both sides of the cerebello-thalamic tract. Current study applied a 15% probability threshold to estimate each cerebello-thalamic WM tract more accurately and to solve the limitation in resolution of our diffusion images and the problem of the crossing fibers caused by the low resolution of our images.

As a result of the tractography, there were subjects that were drawn only on one side or not on either side of the cerebello-thalamic tract. A total of 6 subjects were drawn on one side or not on either side, including 1 OCD patient and 5 HCs, all of whom were excluded from the study. The numbers of participants included in the final analysis were 106 OCD patients (71 male and 35 female, age range 13-48 years) and 105 HCs (66 male and 39 female, age range 17-48 years).

2.5 Statistical analysis

All statistical analyses were conducted using R version 4.0.3 (https://www.r-project.org). For demographics, independent sample t tests or chi-square tests were conducted to examine the difference between patients with OCD and HCs. A significance level of $p < 0.05$ was used for all statistical analyses. To test the significant group differences for diffusion indices of the cerebello-thalamic tract between patients with OCD and HCs, analysis of covariance (ANCOVA) with age and sex as covariates was conducted. The results were corrected for multiple comparisons of the 6 tests (3 diffusion indices × 2 sides of the cerebello-thalamic tract) using the Bonferroni correction.

2.6 Exploring effects of comorbid depressive disorder on diffusion index

To investigate the possible effects of comorbidity, we divided the OCD group into 36 OCD patients with depressive disorder (OCD with depression, 34.0%) and 61

OCD patients without depressive disorder (OCD without depression, 57.5%). Then, to identify group effects, ANCOVA with age and sex as covariates was conducted to test the three diffusion indices, and the results were corrected for multiple comparisons of the 6 tests using the Bonferroni correction.

2.7 DTI lateralization index calculation

To examine the possible hemispheric dominance for the cerebello-thalamic tract, DTI lateralization index (LI) is calculated on FA, MD and RD as follows: LI = (Diffusion index of the Left cerebello-thalamic tract – Diffusion index of the Right cerebello-thalamic tract) / (Diffusion index of the Left cerebello-thalamic tract + Diffusion index of the Right cerebello-thalamic tract) (James et al., 2015). A positive LI value indicates a leftward lateralization, while a negative LI value indicates rightward lateralization (Banfi et al., 2019). To confirm the significance of the lateralization of the corresponding diffusion index, a one-sample t-tests against zero was conducted.

3. Results

3.1 Demographic

Demographic characteristics of the participants, including age, sex, handedness, intelligence quotient (IQ) and education year, were comparable between groups. There were no statistically significant group differences in demographic characteristics between patients with OCD and HCs. Details of demographic are presented in **Table 1**.

3.2 Reconstructed cerebello-thalamic tract

Results for the reconstructed cerebello-thalamic tract are presented in **Figure 2**. The bilateral cerebello-thalamic tracts were successfully reconstructed in 106 patients with OCD and 105 HCs (**Figure 2B** and **2C**). In line with previous studies, current study also shows that the bilateral cerebello-thalamic tracts intersect each other in the midbrain area (**Figure 2A** and **2D**), which is an anatomical characteristic of the cerebello-thalamic tract (H. G. Kwon et al., 2011; Mollink et al., 2016; Nieuwenhuys, 2008; van Baarsen et al., 2016).

3.3 Group differences of diffusion indices

ANCOVA results of the three diffusion indices (FA, MD, and RD) from the reconstructed bilateral cerebello-thalamic tract between the participants with OCD and HCs revealed that MD (F value = 7.98, Bonferroni corrected p value = 0.016)

and RD (F value = 7.31, Bonferroni corrected p value = 0.031) value of the right cerebello-thalamic tract at a 15% threshold were significantly increased in participants with OCD compared with the HCs **(Figure 3)**. However, there was no significant difference for FA in the bilateral cerebello-thalamic tract between groups (Bonferroni corrected p value > 0.999). The results of the ANCOVA comparing three diffusion indices between groups are summarized in **Table 2**. The p values were Bonferroni corrected for 6 tests in these analyses for multiple comparisons.

For comorbid effects of depressive disorder in patients with OCD, there were no significant differences in the three diffusion indices of the bilateral cerebello-thalamic tract between OCD patients with depressive disorder and those without depressive disorder. Thus, current study conclude that compromised white matter integrity of the right cerebello-thalamic tract may not be affected by comorbidity in patients with OCD. Group comparison results of diffusion indices of the cerebello-thalamic tract between patients with OCD presenting with depressive disorder (OCD with depression) and those presenting without depressive disorder (OCD without depression) is presented in **Table 3**.

3.4 DTI lateralization index

This study calculated the LI values of the OCD patients and the HCs for the three diffusion indices of the cerebello-thalamic tract. As shown in **Table 4**, since the LI values for all FA, MD, and RD of HC approached zero, no structural asymmetry was found in HCs (mean LIs = 0.001, -0.001, and -0.002 in the FA, MD, and RD,

respectively). On the other hand, for patients with OCD, FA had a positive LI value (mean LI = +0.024), so FA tended to be lateralized to the left, and MD and RD had a negative LI value (mean LIs = -0.026 and -0.037 in the MD and RD, respectively), so MD and RD tended to be lateralized to the right. As a result of one-sample t-tests against zero, it was found that the LI of the MD (t = -2.76, Bonferroni corrected p = 0.042) and RD (t = -2.88, Bonferroni corrected p = 0.030) was significantly different from zero in patients with OCD, while the LI of the FA was not significantly different from zero in both OCD patients and HCs. The results are summarized in **Table 4**.

4. Discussion

4.1 Summary

Functional dysfunctions between the cerebellum and the thalamus are considered to associate with OC symptoms or cognitive impairment commonly found in OCD patient. Considering that aberrant WM fiber architecture may underlie the functional dysconnectivity, to identify compromised cerebello-thalamic WM integrity in patients with OCD more reliably, this study applied probabilistic tractography. Three diffusion indices (FA, MD, and RD) were evaluated as markers of aberrant WM integrity in the cerebello-thalamic tract and revealed that compromised WM integrity in the right cerebello-thalamic tract was associated with increased MD and RD in OCD patients, whereas FA in the left and right cerebello-thalamic tracts in OCD patients did not differ from that in HCs, suggesting that patients with OCD have immature or degenerative fiber architecture in the right cerebello-thalamic tract or along with deficits in myelination in the underlying WM tract. The results of this study also shown that the cerebello-thalamic tract in OCD patients had rightward structural asymmetry. Overall, current study confirmed aberrant WM integrity in the right cerebello-thalamic tract of medication-free OCD patients, suggesting that these microstructural abnormalities in the right cerebello-thalamic tract may be associated with the pathophysiology of OCD such as OC-symptoms or cognitive dysfunctions.

4.2 Implications of changes in diffusion indices

In current study, consistent with the hypothesis, OCD patients showed significantly higher MD and RD in the right cerebello-thalamic tract than HCs after controlling age and sex, whereas there was no significant group difference in FA between OCD patients and HCs. Conventionally, unchanged FA is regarded as equivalent to WM integrity (Jones, Knosche, & Turner, 2013; Silk et al., 2013). However, since FA is a relative measure of diffusivity, if the diffusion changes proportionally along the three eigenvectors, the sensitivity of FA may decrease, so FA alone is not enough to determine the WM integrity of the tract (Van Camp et al., 2012). In contrast, in the same condition, MD and RD increases because net diffusivity increases (Figley et al., 2021). Thus, considering that FA alone cannot account for the full tensor shape, MD and RD, which are absolute measures that can provide quantitative information about WM integrity changes, should be considered in addition to FA. Increased MD can be explained by expansion of the extracellular space and increased water diffusivity due to abnormal cytoarchitecture or neuroinflammation, suggesting immaturity or degeneration of the cerebello-thalamic tract in patients with OCD (Bennett et al., 2010; Blain et al., 2006; Lochner et al., 2012; Song et al., 2002). In addition, increased RD usually indicates damage to myelination of axons in WM, suggesting dys- or demyelination of axons or altered myelin integrity in OCD patients (Harsan et al., 2006; Song et al., 2003). Therefore, although it is difficult to conclude that WM integrity of the cerebello-thalamic tract is aberrated in OCD patients with intact FA values, the results of this study, which showed an increase in MD and RD in

the right cerebello-thalamic tract, may suggest increased overall water diffusivity due to abnormal cytoarchitecture or neuronal inflammation in the right cerebello-thalamic tract, represented by increased MD, and dys- or demyelination of axons or altered myelin integrity, represented by increased RD, may affect cerebello-thalamic WM architecture of patients with OCD.

Furthermore, in this study, diffusion index changes were observed only in the right cerebello-thalamic tract, and no diffusion index changes were observed in the left cerebello-thalamic tract. To investigate possible lateralization in the cerebello-thalamic tract of patients with OCD, LI value for diffusion indices between left and right cerebello-thalamic tract was calculated (James et al., 2015). As a result of the analysis, MD and RD of the cerebello-thalamic tract tended to be significantly lateralized to the right in OCD patients, while no lateralization was found for FA. These results of this study confirmed that patients with OCD had rightward structural asymmetry of the cerebello-thalamic tract. Although functional and structural lateralization of the bilateral cerebello-thalamic tract in OCD patients is still poorly understood (Baillieux et al., 2010; Kim, Im, Kim, & Park, 2019), considering previous functional studies that alteration in the right cerebello-thalamic connection was associated with cognitive dysfunction associated with the left hemisphere such as language difficulties (Gottwald, Wilde, Mihajlovic, & Mehdorn, 2004; Hokkanen, Kauranen, Roine, Salonen, & Kotila, 2006; Marien, Engelborghs, Fabbro, & De Deyn, 2001; Marien et al., 1996), the current findings suggest that compromised right cerebello-thalamic tract WM microstructure may underlie the cognitive dysfunction of OCD patients.

4.3 Implications of current findings compared to previous studies

To date, two DTI studies using whole-brain TBSS have reported cerebello-thalamic WM abnormalities in OCD patients (Jayarajan et al., 2012; Tikoo et al., 2021). In line with the current findings, Jayarajan et al. reported that OCD patients showed increased RD in the WM region overlapping with the right cerebello-thalamic tract compared to HCs, but no significant group differences were found in FA values (Jayarajan et al., 2012). On the other hand, Tikoo et al. reported significantly lower FA and higher MD in WM regions overlapping with the left cerebello-thalamic tract in OCD patients than in HCs (Tikoo et al., 2021). The discrepancy between this study and that by Tikoo et al. may be due to differences in imaging analysis technique (i.e., tractography vs. TBSS) and sample sizes (i.e., 106 OCD patients in this study vs. 10 OCD patients in the study by Tikoo et al.). To address the issues, the probabilistic tractography approach was used in this study, since it allows better delineation of the WM tract than the whole brain TBSS approach; it reduces the partial volume effects and analyzes specific WM tracts as a whole rather than limiting it to small regions overlapping WM tracts. In addition, previous studies may have low statistical power in that they conducted research a relatively small number of subjects (Boedhoe et al., 2017; Lin, Weng, Xie, Wu, & Lei, 2011; Melicher et al., 2015; Piras et al., 2021). Thus, the results of the present study using probabilistic tractography in a relatively large number of OCD

patients may better describe cerebello-thalamic tract WM abnormalities in OCD patients.

Furthermore, Previous functional MRI studies have consistently reported that altered cerebello-thalamic connectivity was related to cognitive impairments found in OCD patients (Buckner et al., 2011; Eng et al., 2015; Stoodley & Schmahmann, 2009). In addition, previous functional connectivity studies on patients with OCD have shown that functional networks, including cerebello-thalamic circuits, were associated with OC symptom severity or OC-like behavior (Fan et al., 2017; Tikoo et al., 2021; Xia et al., 2019). These previous studies highlight the dysconnectivity between the cerebellum and the thalamus in OCD patients and the involvement of the cerebello-thalamic circuit to abnormal functioning in patients with OCD. The current study findings, which reported increased MD and RD values in the right cerebello-thalamic tract in OCD patients, are significant in that it may provide structural background for those functional studies. Furthermore, in line with the results of previous structural MRI studies (Jayarajan et al., 2012; Tikoo et al., 2021), current studies have shown that the cerebello-thalamic tract WM microstructure is aberrated in patients with OCD. Therefore, although future studies should focus on the direct association between OC symptomatology or cognition and compromised WM structural abnormalities of the cerebello-thalamic tract, considering that previous functional studies have shown that abnormal dysfunctions in the cerebello-thalamic connection are related to OC-like behavior and OC symptoms, current study suggest that microstructural

abnormalities in the right cerebello-thalamic tract may underlie OCD pathophysiology.

4.4 Limitations

This study has several limitations. First, the results of this study may be limited by MRI acquisition. A single B0 image and non-isotropic voxel shape might have had a slight influence on the process of WM tract reconstruction, such as fiber orientation or diffusivity mapping. During image acquisition, cardiac pulsation was not controlled, which could induce body movements. However, to solve this problem, the subjects with images with critical artifacts through the visual inspection of every participant's DWI were excluded in this study. Second, current study did not perform correlation analysis between altered diffusion indices and OC symptom severity score or neurocognitive function test results. Thus, interpretation regarding the current study finding of an underlying structural abnormality of OCD pathophysiology, such as symptoms or cognitive dysfunction, should be further supported by correlation analysis in future study.

4.5 Conclusion

In conclusion, this study demonstrated that MD and RD of the right cerebello-thalamic tract in patients with OCD were significantly higher than those of HCs. Although there was no change in FA representing WM integrity, the increases in other diffusivity measures could indicate that the microstructure of the right cerebello-thalamic WM connections is possibly impaired, such as through axonal

degeneration or demyelination. Furthermore, based on previous fMRI studies for OCD-related behaviors and cognitive functions, the impaired WM microstructure of the right cerebello-thalamic tract may underlie not only altered activity patterns between the cerebellum and the thalamus but also their cognitive function and behavioral dysfunction in OCD patients. Using probabilistic tractography, we reconstructed cerebello-thalamic WM connections more finely in individual subjects and subsequently measured diffusion indices. We only included medication-free patients with OCD to minimize confounding effects of psychotropic medications on WM structures as well as using relatively large sample (Benedetti et al., 2013). Therefore, this study confirmed that the WM integrity of the right cerebello-thalamic tract is significantly altered in OCD patients, and since aberrant WM structure between the cerebellum and the thalamus may reflect their neural dysfunction as well as functional dysfunction, thus suggesting an anatomical underpinning of behavioral impairments and cognitive dysfunctions in patients with OCD.

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Tables

Table 1. Demographic and clinical characteristics of the participants

Variable		OCD (n = 106)	HCs (n = 105)	χ^2/t	*p*
Age (year)		24.9 ± 6.9	25.3 ± 6.5	-0.35	0.729
Sex (Male/Female)		71/35	66/39	0.63	0.533
IQ		112.7 ± 12.5	109.7 ± 15.8	1.56	0.122
Handedness (Left/Right)		7/99	1/104	-0.53	0.595
Education (year)		14.2 ± 2.3	14.2 ± 2.1	-0.09	0.931
Duration of illness (year)		6.8 ± 5.7			
Y-BOCS	Total	26.6 ± 6.3			
	Obsession	14.0 ± 3.0			
	Compulsion	12.5 ± 4.3			
HAM-D		11.8 ± 6.2			
HAM-A		10.9 ± 6.0			
Comorbidity	None	61 (57.5%)			
	Depressive disorder	36 (34.0%)			
	Bipolar disorder	6 (5.7%)			
	Personality disorder	3 (2.8%)			

The data are presented as mean ± standard deviation.

Y-BOCS Yale Brown obsessive-compulsive scale, **HAM-D** Hamilton rating scale for depression, **HAM-A** Hamilton rating scale for anxiety, **OCD** Obsessive-compulsive disorder patients, **HCs** Healthy controls (age-, sex-, and handedness-matched)

Table 2. Fractional anisotropy, mean diffusivity and radial diffusivity values of the bilateral cerebello-thalamic tract in patients with OCD and HCs

Diffusion indices		OCD (n = 106)	HCs (n = 105)	F	p	Bonferroni-corrected p
FA	Left	0.495 ± 0.051	0.487 ± 0.058	1.16	0.283	>0.999
	Right	0.474 ± 0.067	0.485 ± 0.055	1.75	0.188	>0.999
MD (10^{-3} mm^2/s)	Left	0.913 ± 0.139	0.911 ± 0.117	0.00	0.952	>0.999
	Right	0.964 ± 0.156	0.911 ± 0.106	7.98	0.003	0.016*
RD (10^{-3} mm^2/s)	Left	0.661 ± 0.139	0.664 ± 0.127	0.03	0.862	>0.999
	Right	0.718 ± 0.170	0.666 ± 0.116	7.31	0.005	0.031*

The data are presented as mean ± standard deviation. * Bonferroni corrected $p < 0.05$.

OCD obsessive-compulsive disorder patients, **HCs** healthy controls (age-, sex-, and handedness-matched), **FA** fractional anisotropy, **MD** mean diffusivity, **RD** radial diffusivity

* Denotes significant group differences obtained via ANCOVA. Results are Bonferroni corrected at $p < 0.05$ for multiple comparisons for 6 tests.

Table 3. Comparison of diffusion indices of the cerebello-thalamic tract between patients with OCD presenting with depressive disorder and those presenting without depressive disorder

Diffusion indices		OCD with depression	OCD without depression	*F*	*p*	Bonferroni-corrected *p*
FA	Left	0.501 ± 0.041	0.492 ± 0.055	0.75	0.389	>0.999
	Right	0.478 ± 0.075	0.472 ± 0.064	0.21	0.652	>0.999
MD (10^{-3} mm^2/s)	Left	0.891 ± 0.009	0.923 ± 0.158	1.22	0.272	>0.999
	Right	0.959 ± 0.181	0.966 ± 0.142	0.05	0.817	>0.999
RD (10^{-3} mm^2/s)	Left	0.642 ± 0.010	0.671 ± 0.164	0.97	0.327	>0.999
	Right	0.713 ± 0.197	0.724 ± 0.153	0.10	0.753	>0.999

The data are presented as the mean ± standard deviation.

OCD obsessive-compulsive disorder patients, **OCD with depression** patients with OCD presenting with depressive disorder, **OCD without depression** patients with OCD without depressive disorder, **FA** fractional anisotropy, **MD** mean diffusivity, **RD** radial diffusivity

Table 4. Lateralization index value of the fractional anisotropy, mean diffusivity, and radial diffusivity in the patients with OCD and HCs

Lateralization index		Mean	Standard deviation	*t*	*p*	Bonferroni-corrected *p*
LI for FA	OCD	0.024	0.095	2.60	0.011	0.066
	HCs	0.001	0.081	0.14	0.891	>0.999
LI for MD	OCD	-0.026	0.096	-2.76	0.007	0.042*
	HCs	-0.001	0.080	-0.09	0.930	>0.999
LI for RD	OCD	-0.037	0.134	-2.88	0.005	0.030*
	HCs	-0.002	0.113	-0.20	0.838	>0.999

The data are presented as the mean ± standard deviation. Negative LI value indicates right-hemispheric dominance.

OCD obsessive-compulsive disorder patients, **HCs** healthy controls, (age-, sex-, and handedness-matched), **LI** lateralization index, **FA** fractional anisotropy, **MD** mean diffusivity, **RD** for radial diffusivity

* Denotes significant group differences obtained via one-sample t-test against zero. Results are Bonferroni corrected at $p < 0.05$ for multiple comparisons for 6 tests.

Figures

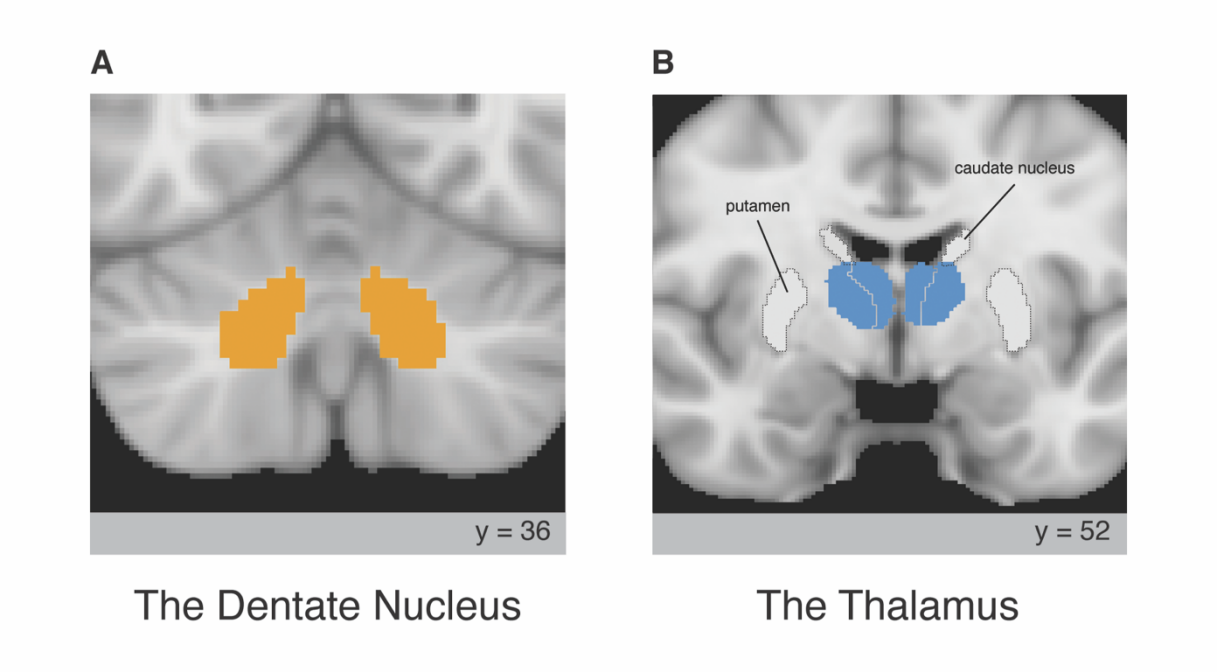

Figure 1. Regions of interest (ROIs) for reconstructing the bilateral cerebello-thalamic tract by using probabilistic tractography, overlaid on the 1 mm T1-weighted Montreal Neurological Institute (MNI) template. (A) The ipsilateral dentate nucleus, one of the deep cerebellar nuclei, depicted in yellow was used as seed masks. (B) The contralateral thalamus, taken from the Oxford Thalamic Connectivity Atlas,

pictured in blue, was chosen as waypoint as well as stop region. For the left cerebello-thalamic tract, the left dentate nucleus was chosen as seed region and right thalamus was chosen as waypoint as well as stop region. For the right cerebello-thalamic tract, the right dentate nucleus was used as seed region and left thalamus was chosen as waypoint and stop mask.

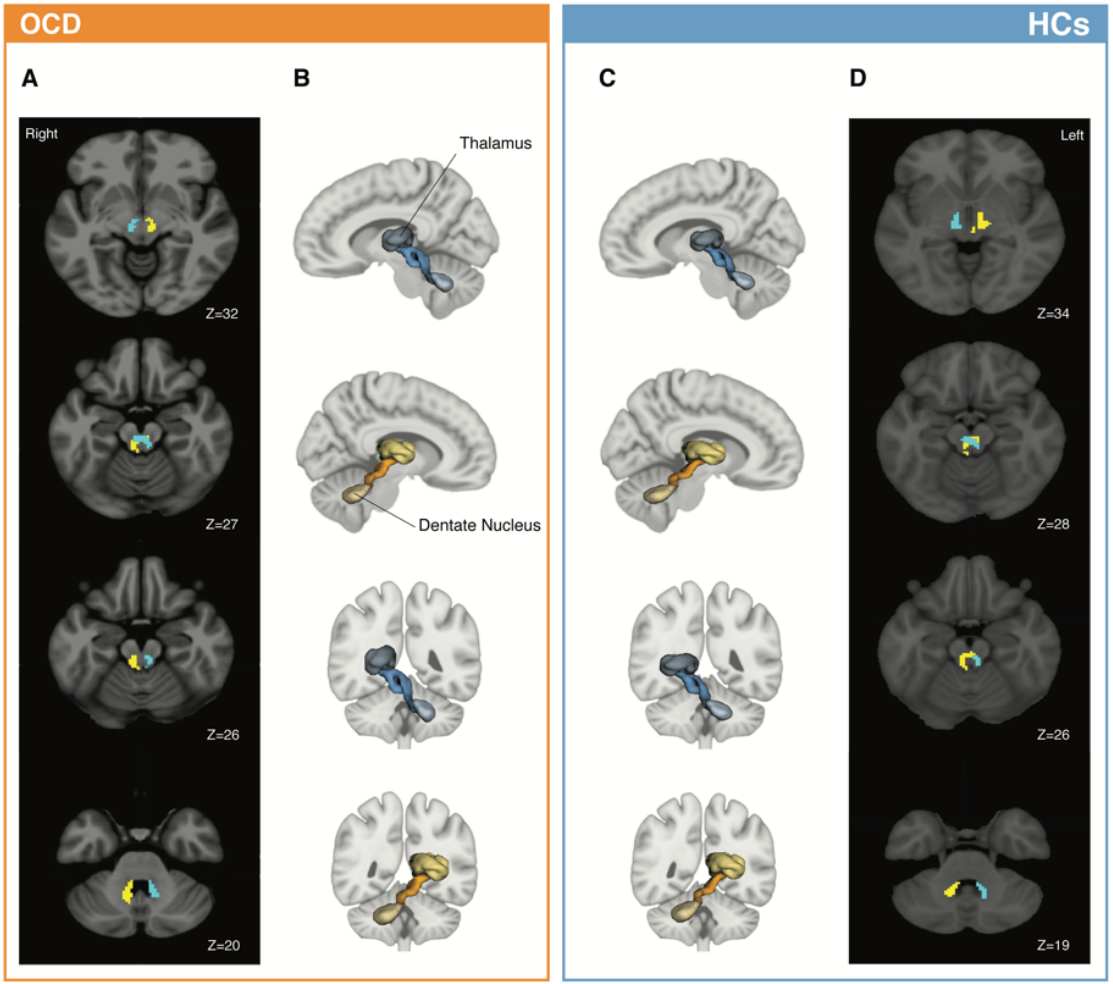
OCD
HCs
A
B
C
D
Right
Left
Thalamus
Dentate Nucleus
Z=32
Z=27
Z=26
Z=20
Z=34
Z=28
Z=26
Z=19

Figure 2. Tractography results of the bilateral cerebello-thalamic tract in both OCD patients and healthy controls (HCs). The left column depicted in yellow presents tractography results of the OCD patients and the right column shown in blue shows tractography results of the HCs. The left cerebello-thalamic tract is depicted in blue, and the right cerebello-thalamic tract is pictured in yellow. The bilateral cerebello-thalamic tracts were applied 15% probability threshold to estimate white matter tract more precisely. All tracts were overlaid on the 1 mm T1-weighted MNI template. (A) The left and right cerebello-thalamic tract of the OCD patients were described on axial planes. The anatomical feature of the cerebello-thalamic tract where the left and right cerebello-thalamic tract intersect in the mid-brain area was presented at Z = 27. (B) The bilateral cerebello-thalamic tract of patients with OCD were 3D-reconstructed on sagittal planes. (C) The 3D-reconstructed left and right cerebello-thalamic tract of HCs were presented on sagittal planes. (D) The bilateral cerebello-thalamic tract of HCs was described on axial planes. The left and right cerebello-thalamic tract of HCs decussated in mid-brain at Z = 28.

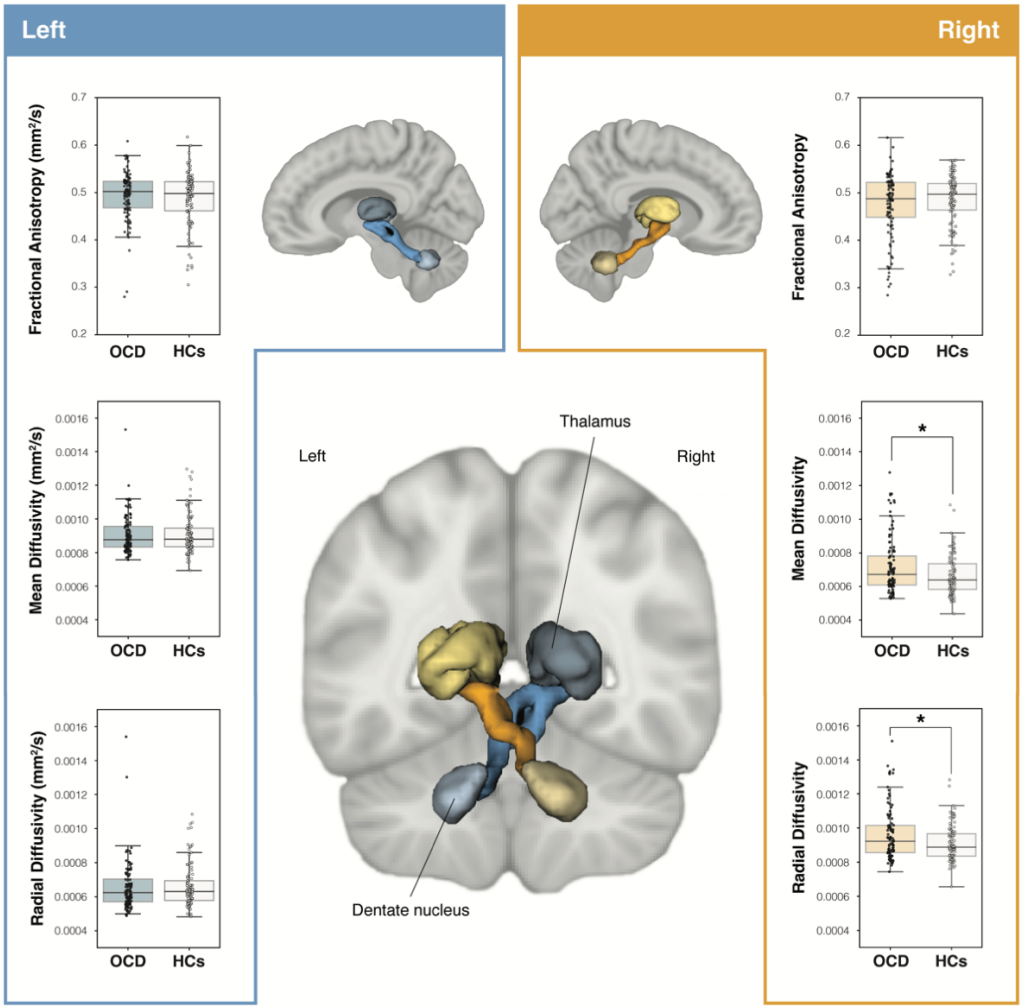
Left
Right
Fractional Anisotropy (mm²/s)
Mean Diffusivity (mm²/s)
Radial Diffusivity (mm²/s)
OCD
HCs
Thalamus
Left
Right
Dentate nucleus
Fractional Anisotropy
Mean Diffusivity
Radial Diffusivity
*

Figure 3. The results of statistical analysis of fractional anisotropy, mean diffusivity, and radial diffusivity of bilateral cerebello-thalamic tract in patients with OCD and healthy controls (HCs). The left column, depicted in blue, shows the group effects on diffusion indices of the left cerebello-thalamic tract and the right column, shown in yellow, shows the group effects on the diffusion index of the right cerebello-thalamic tract. The analysis of covariance (ANCOVA) results with age and sex as covariates were corrected with the Bonferroni test for multiple comparisons and were presented as "*" ($p < 0.05$) on each box plot. Sagittal scenes of 3D-reconstructed cerebello-thalamic tracts in the left (blue) and right (yellow) hemispheres were presented at the top of each column. The axial view of the bilateral cerebello-thalamic tracts was shown in the center. As a result of ANCOVA, mean diffusivity and radial diffusivity of the right cerebello-thalamic tract in OCD patients were significantly higher than that of HCs, and there was no group difference in fractional anisotropy.

국문 초록

소뇌-시상관은 소뇌와 시상을 연결하는 소뇌의 유일한 원심성 백질 다발로, 강박 장애 환자에서 흔히 손상되었다고 알려진 고위 인지기능에 필수적인 역할을 하는 것으로 알려져 최근 많은 관심을 받고 있다. 기존의 기능적 뇌영상 연구는 강박 장애 환자에서 소뇌와 시상 사이의 연결이 기능적으로 손상되어 있으며, 이러한 소뇌-시상 회로의 기능 이상이 강박 장애 증상 심각도와 관련이 있다는 것을 보이며 소뇌와 시상 사이의 비정상적인 연결성이 강박 장애의 병태생리와 관련이 있음을 보였다. 그러나 강박 장애 환자의 소뇌-시상 연결성의 기능적 이상에 대한 기저가 될 수 있는 소뇌-시상관 백질 무결성에 대해서는 아직까지 충분한 이해되지 않았다. 따라서, 본 연구는 약물 효과를 배제한 강박 장애 환자에서 소뇌-시상관의 백질 무결성 손상 여부를 규명하는 것을 목표로 한다. 본 연구에는 106 명의 약물 효과를 배제한 강박 장애 환자와 나이와 성별, 지능 지수, 손잡이, 교육 년 수가 매칭된 105 명의 정상 대조군이 연구에 참여하였으며, 모든 참여자에서 확산 텐서 이미지와 T1 이미지를 수집하였다. 그 후 정확한 해부학적 특징을 반영한 소뇌-시상관을 재구성하기 위해 확률적 트랙토그래피를 적용하였고, 재구성된 양쪽 소뇌-시상관에서 세 가지 확산 지수 (분위 이방성 [FA], 평균 확산성 [MD], 방사형 확산성 [RD])를 측정한 후 강박 장애군과 정상 대조군간 차이가 있는지 알아보기 위해 분산분석을 진행하였다. 분석 결과, 강박 장애 환자들은 정상 대조군과 비교했을 때 우측 소뇌-시상관에서 평균 확산성과 방사형 확산성이 유의하게 증가하였으며, 두 그룹 간 분위 이방성에는 유의한 차이가 없었다. 또한, 강박 장애 환자의 오른쪽 소뇌-시상관의 평균 확산성과 방사형 확산성은 유의하게 오른쪽으로 편측된 것을 확인할 수 있었다. 본 연구의 결과는 강박 장애 환자의 소뇌-시상 회로의

기능적 이상에 대해 근본적인 구조적 이상이 있음을 보였다. 이러한 연구 결과는 강박 장애 환자의 소뇌-시상 회로의 기능적 손상에 대해 보다 근본적인 구조적 이상이 있음을 나타내며, 더 나아가 우측 소뇌-시상관의 손상된 백질 미세 구조가 강박 장애 환자의 강박 유사 행동 또는 인지 기능 장애와 같은 강박 장애 병태생리의 기초가 될 수 있음을 시사한다.

주요어: 강박증; 소뇌-시상관; 백질; 확산 텐서 영상, 강박증, 확률적 트랙토그래피

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