#### **ORIGINAL RESEARCH**



# Whole brain volume and cortical thickness abnormalities in Wilson's disease: a clinical correlation study

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#### Abstract

Wilson's disease (WD) is an inherited autosomal recessive disorder of copper metabolism, and its neurological and neuropsychiatric manifestations are associated with copper accumulation in brain. A few neuroimaging studies have shown that gray matter atrophy in WD affects both subcortical structures and cortex. This study aims to quantitatively evaluate the morphometric brain abnormalities in patients with WD in terms of whole brain volume and cortical thickness and their associations with clinical severity of WD. Thirty patients clinically diagnosed as WD with neurological manifestations and 25 healthy controls (HC) were recruited. 3D T1-weighted images were segmented into 276 whole-brain regions of interest (ROIs) and 68 cortical ROIs. WD-vs-HC group comparisons were then conducted for each ROI. The associations between those morphometric measurements and the Global Assessment Scale (GAS) score for WD were analyzed. Compared with HC, significant WD-related volumetric decreases were found in the bilateral subcortical nuclei (putamen, globus pallidus, caudate nucleus, substantia nigra, red nucleus and thalamus), diffuse white matter and several gray matter regions. WD patients showed reduced cortical thickness in the left precentral gyrus and the left insula. Further, the volumes of the right globus pallidus, bilateral putamen, right external capsule and left superior longitudinal fasciculus were negatively correlated with GAS. Our results indicated that significant WD-related morphometric abnormalities were quantified in terms of whole-brain volumes and cortical thicknesses, some of which correlated significantly to the clinical severity of WD. Those morphometrics may provide a potentially effective biomarker of WD.

Keywords Wilson's disease · Structural MRI · Whole brain volume · Cortical thickness

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# Introduction

Wilson's disease (WD) is an inherited autosomal recessive disorder of copper metabolism leading to copper accumulation in hepatocytes and extrahepatic organs (Ala et al. 2007; Członkowska et al. 2018). While neurological and neuropsychiatric manifestations related to WD are classically associated with copper accumulation in brain (Bandmann et al. 2015).

During the past several years, there have been a very few quantitative researches on WD-related brain abnormalities using advanced neuroimaging techniques. Two voxel-based morphometry (VBM) studies have demonstrated that the volumes of grey matter (GM) in the frontal, occipital and temporal lobes, basal ganglia, cerebellum and thalamus were decreased in WD patients (Hu et al. 2017; Stezin et al. 2016). However, VBM has been shown to be sensitive to whole brain image registration errors (Ashburner 2009), especially in cortical regions wherein the topology varies hugely from subject to subject. It is challenging to distinguish whether the abnormality patterns identified from VBM are real or just noises induced by the inaccurate image registration.

As an alternative to VBM, whole brain segmentation based on volumetric analysis has been applied, which is more intuitive and more robust. Volumetric analysis in this study was conducted by using a multi-atlas pipeline built upon a twolevel Bayesian parameter estimation algorithm called the Multi-Atlas Likelihood Fusion (MALF) algorithm (Tang et al. 2013; Wang et al. 2013) which overcomes the shortness of VBM analysis method (or has a higher accuracy in calculating the brain volume and cortical thickness). Whole brain segmentation has been applied to a variety of brain disease analyses, such as Alzheimer's disease and Parkinson's disease (Liu et al. 2019; Chen et al. 2017; Kamagata et al. 2017), but not WD. In addition to whole brain volumes, cortical thicknesses are also important brain morphometrics to investigate (Fischl et al. 2004). However, no quantitative MRI study has been performed for the investigation of cortical thickness abnormality patterns in WD.

Although WD was first described more than a century ago, the exact changes of volume and cortical thickness in the whole brain about how WD will affect brain are far from clear. And there have been a very few quantitative researches on WD-related brain abnormalities using advanced neuroimaging techniques during the past several years. Our purpose of this study is to focus on the new techniques and to explore their utility in WD. We hope this study can offer a priori for the further whole brain analyses in WD and further explore the imaging biomarkers to assess disease progression. In this study, we hypothesize that there are whole brain volume abnormalities, including GM and white matter (WM), and cortical thickness abnormalities in the pathology of WD and the identified morphometric abnormalities significantly correlate with clinical severity of WD.

## Methods

#### **Subjects**

Thirty patients with WD (18 males, 12 females, mean age: 27.93  $\pm$  5.37 years, range: 18–37 years) at an untreated stage with neurological manifestations as confirmed by clinical and laboratory examinations, and 25 healthy controls (HC, 15 males, 10 females, mean age: 28.12  $\pm$  5.62 years, range: 18–38 years) with age, gender and years of education matched were enrolled in this study. All subjects were right-handed and underwent a series of neurological tests, including the Global Assessment Scale for WD (GAS for WD)(Aggarwal et al. 2009), the Mini-Mental State Examination (MMSE)(Tombaugh and McIntyre 1992), the Hamilton Depression Rating Scale (HAMD)(Hamilton 1960) and the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton 1959). Diagnostic criteria (Ferenci et al. 2003) of

WD include a ceruloplasmin concentration less than 0.2 g/L, a 24-h urinary copper excretion greater than 100 µg, the presence of K-F rings on slit-lamp examination and clinical symptoms (such as the presentation of extrapyramidal symptoms and signs, with dysarthria and tremor, and remarkable impairment of liver function). Two experienced neurologists scored each patient's clinical symptoms by GAS. The disease duration time of each patient, from the time of disease onset (self-reported) to the time of MRI scanning, was recorded. None of the patients had a history of neurological diseases other than WD. For HC, all participants were enrolled from college students or society officers and those who failed to meet the following research criteria points were excluded: (a) without central nervous system diseases, mental diseases, nor other serious diseases; (b) the MMSE, HAMD and HAM-A scores within the normal range (adjusted for age, sex, and education); and (c) a GAS score of 0. Table 1 summarized the clinical and demographic characteristics of all subjects. This study was approved by the Medical Ethical Committee of The First Affiliated Hospital of Sun Yat-sen University. Informed consent was obtained from all participants.

#### **MRI data acquisition**

All MRI scans were performed on a 3.0 T MRI scanner (Magnetom Trio, Siemens Healthcare, Erlangen, German), using a 12-channel head coil. For each participant, the T1-weighted brain image was acquired using a 3D magnetization prepared-rapid acquisition gradient echo (MP-Rage) sequence. Scanning parameters are shown as follows: TR = 1750 ms, TE = 2.88 ms, TI = 900 ms, matrix =  $384 \times 384$ , FOV = 260 mm × 260 mm, voxel size = 0.7 mm × 0.7 mm × 0.7 mm (256 slices and without slice gap), flip angle = 9°, and the acquisition time was 4.21 min. All MRI images were visually inspected by one experienced neurologist and one neuroradiologist.

#### Whole-brain volumetric segmentation

A multi-atlas pipeline (a module implemented at *www. mricloud.org*) was used to segment T1-weighted images into a total of 276 whole-brain anatomical ROIs. In the current study, we used 45 atlases (available at the MriCloud website) which are in a similar age range as that of our 55 participants. Details of the selected atlas set, and their label definitions have been described elsewhere (Mori et al. 2016). All segmentation results were examined visually and verified repeatedly to guarantee the accuracy of each segmentation. Then the volumetric measurement of each ROI was calculated as the total number of voxels within the corresponding ROI multiplied by the voxel resolutions (0.7 mm × 0.7 mm × 0.7 mm). The volume decrease rate of a structure was defined as  $(V_{HC}-V_{WD}) / V_{HC} \times 100\%$ , with V representing the average volume of a specific group.

 Table 1
 Clinical and

 demographic characteristics of all
 subjects enrolled in this study

Characteristics	WD ( $N = 30$ )	HC $(N = 25)$	P <sup>a</sup> values
Gender (male/female)	18/12	15/10	0.608
Age (years)	$27.93 \pm 5.37$	$28.12\pm5.62$	0.900
Education (years)	$13.10\pm2.23$	$13.84 \pm 2.69$	0.270
Handedness (right/left)	30/0	25/0	_
Disease duration (months)	$43.87 \pm 19.51$	_	_
WD types	neurologic	_	_
Family history	100.00%	_	_
KF ring present	100.00%	_	_
24 h urinary copper excretion (µg)	$785.80 \pm 424.91$	_	_
Ceruloplasmin (g/L)	$0.64\pm0.40$	_	_
GAS score for WD	$15.64 \pm 6.64$	$0.00\pm0.00$	_
MMSE score			
Mean (SD)	$28.30\pm2.51$	$29.12 \pm 1.09$	0.133
N% <sup>b</sup>	86.67%	100.00%	0.135
HAMD score			
Mean (SD)	$10.90 \pm 5.71$	$1.88\pm2.20$	< 0.001
N% <sup>b</sup>	40.00%	100.00%	< 0.001
HAM-A score			
Mean (SD)	$13.93\pm7.35$	$1.32\pm1.70$	< 0.001
N% <sup>b</sup>	16.67%	100.00%	< 0.001

Data are mean  $\pm$  standard deviation. Statistical significance was set to P < 0.05

Normal reference range: 24 h urinary copper excretion,  $15-30 \mu g$ ; Ceruloplasmin, 0.2-0.4 g/L; MMSE score,  $\geq 23$  for high school education and  $\geq 24$  for college education; HAMD score, 0-8; HAM-A score, 0-7

WD Wilson's disease, HC Healthy controls, N Number, KF Kayser-Fleischer; —, Not available, MMSE Mini-Mental State Examination

<sup>a</sup> *P* values for continuous variables derived from Student's t test; categorical variables from Chi-square test <sup>b</sup> Proportion of normal subjects

## Surface-based cortical thickness measurement

Surface-based cortical thickness measurements for 68 cortical ROIs were automatically obtained from the FreeSurfer software (version 5.0). The surface-based stream comprised in the Freesurfer analysis pipeline includes some preliminary steps as follows: motion correction, affine registration to Talairach atlas, intensity normalization, skull stripping, automatic subcortical segmentation including neck removal (Desikan et al. 2006; Fischl et al. 2004), segmentation of WM and GM structures (http://surfer.nmr.mgh.harvard.edu/fswiki) and so on. After that, the mid brain is cut from the cerebrum and the hemispheres are separated from each other in step Cut/Fill. The subsequent steps involve tessellation of GM-WM boundary (Dale et al. 1999), original surface smoothing, inflation for minimize metric distortion, automatic topology correction, and surface formation in which the GM-WM boundary and pial surface are estimated and optimized. The shortest distance between the pial surface and the GM-WM boundary at each vertex across the cortical mantle was calculated as the value of the cortical thickness. Estimated total intracranial volume (eTIV) and cortical thickness were respectively extracted from the aseg.stats and lh/rh.aparc.stats file, which are part of the results obtained from the "recon-all" batch command.

For cortical thickness estimation and analysis, all data were processed using the same version of FreeSurfer software, the details of which have been described elsewhere (Fischl and Dale 2000; Fischl et al. 1999). It should be noted that no manual correction was made to any of the Freesurfer results to ensure a valid analysis. However, a visual inspection was conducted to check the quality of the FreeSurfer results.

#### Group comparison analysis

To assess whether there is any significant WD-vs-HC difference in each volume measurement and each cortical thickness measurement, inner-group comparisons were conducted using a linear regression model (Tang et al. 2014), namely  $J_k(s)$ 

 $= \alpha_k + \beta_k Y(s) + \sum_{cov} \alpha_{cov} X_{cov}(s) + \varepsilon_k(s), \text{ where } J_k(s) \text{ denotes a specific measurement (volume or cortical thickness)} of specific structures of interest k for subject$ 

s,  $X_{cov}(s)$  represents the covariate information of participants (for this study, eTIV, age, gender and years of education were used as covariates),  $\varepsilon_k(s)$  denotes a Gaussian noise structure  $N(0, \sigma_k^2)$  and Y(s) is a binary group variable (0 for HC, and 1 for WD). We tested the null hypothesis  $H_0$ :  $\beta_k = 0$  against the general hypothesis  $H_0: \beta_k \neq 0$  simultaneously for all volume measurements and all cortical thicknesses. The statistical significance of each group comparison was quantified using a P value from Fisher's method of randomization. In both the whole-brain volumetric analysis and the cortical thickness analysis, multiple comparison correction was carried out by controlling the familywise error rate (FWER) at a level of 0.05 based on the maximum statistic method. Accordingly, a two side of P value <0.05 is considered statistical significance in the volumetric analysis, and a two side of P value < 0.0013 is considered statistical significance in the cortical thickness analysis.

#### **Statistical analysis**

Statistical analyses were performed with R (Version 3.3.2 for Windows, Comprehensive R Archive Network, http://cran.rproject.org). The Shapiro-Wilk test was used for analysis of normal distribution; demographic and clinical data were analyzed by Student's t test for continuous variables and the  $\chi 2$  test for categorical variables. Pearson correlation coefficient analysis was used to assess the correlation between each morphometric measurement (volume and cortical thickness) and the GAS score, MMSE score, HAMD score, HAM-A score, disease duration, 24 h urinary copper excretion, and ceruloplasmin. The significance level was set to be 0.05. Multiple comparison correction by controlling the FWER at a level of 0.05 was conducted in the correlation analysis, resulting in a two side of *P* value <0.0025 is considered statistical significance.

# Results

#### Whole-brain volume analysis

After FWER correction, significant WD-related volumetric decreases were found in the subcortical nuclei, including the bilateral putamen, globus pallidus, caudate nucleus, substantia nigra, red nucleus and thalamus (P < 0.0001). Diffuse WM regions and some GM regions (bilateral cingulate gyrus and bilateral superior frontal gyrus) were also found to have significant volumetric decreases in the WD group. In addition, significant volumetric increases were found in the lateral ventricle, the third ventricle, the sylvian fissure and insular sulcus (P < 0.0001) (Fig. 1). More details regarding the whole-brain volumetric differences between the two groups are presented in the Appendices Table 3.

In terms of the volume change rate, we found that the bilateral superior fronto-occipital fasciculus (right: 53.29%, left: 44.59%), putamen (right: 48.32%, left: 47.15%), external capsule in the claustrum (right: 37.52%, left: 42.88%), substantia nigra (right: 38.24%, left: 35.09%), left globus pallidus (37.13%) and left nucleus accumbens (34.66%) were the top ten structures exhibiting the highest volume change rates. For detailed results, please see the Appendices Table 3.

## **Cortical thickness analysis**

After FWER correction, patients with WD showed decreased mean cortical thickness in the left precentral gyrus and the left insula (P < 0.0013), as shown in Fig. 2 and Table 2. There were no significant differences in the eTIV and cortical thickness of other structures in patients with WD.

#### **Correlation analysis**

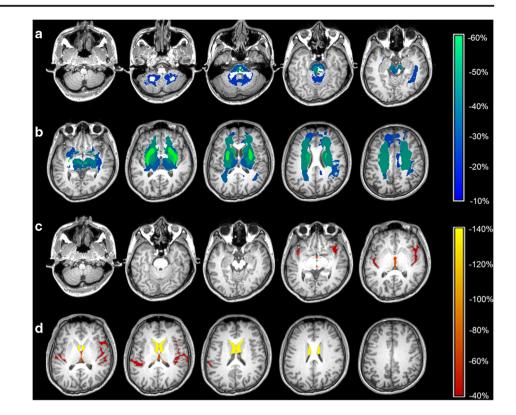
For the whole-brain volumetric measurements, statistically significant correlations to the GAS score were found in the left putamen (r = -0.691, P < 0.001) and right putamen (r = -0.729, P < 0.001), in the WD group, after FWER correction at a threshold of P = 0.0025 (Fig. 3). No significant correlations were found between other clinical characteristics and volume measurements. No significant correlations were found among the GAS score, MMSE score, HAMD score, HAM-A score, disease duration, 24 h urinary copper excretion, ceruloplasmin and any of the 68 cortical thicknesses in patients with WD.

## Discussion

In the present study, we quantitatively investigated WDrelated abnormality patterns of the volumes of 276 wholebrain ROIs and cortical thicknesses of 68 cortical ROIs. Our study yielded three findings: Firstly, volumetric analysis demonstrated significant atrophy of various brain structures and significant expansion of the ventricular system in patients with WD. The brain atrophy was prominent in the basal ganglia, especially the lenticular nucleus (globous pallidus and putamen). Secondly, cortical thickness analysis showed that patients with WD were characterized by cortical thinning in the left precentral gyrus and the left insula. Finally, the volumes of bilateral putamen were significantly correlated with clinical severity in patients with WD.

In agreement with previous neuroimaging studies in Wilson's disease (Li et al. 2018; Stezin et al. 2016; Zou et al. 2019), we observed similar structural changes in the basal ganglia, cerebellum, midbrain, pons, diffuse WM regions and some GM regions in our patients. These signal changes are reported to be due to edema, neuronal necrosis,

**Fig. 1** Volumetric comparison results between WD and HC groups. Fig (**a**, **b**): Maps of whole brain atrophy patterns. Fig. (**c**, **d**): Maps of whole brain expansion patterns. The color bar denotes the volume decrease rate (%) at regions that had survived the FWER correction



gliosis, demyelination, or cystic degeneration of neurons due to copper overload, which leading to the atrophy of the corresponding structures and then causing the corresponding clinical symptoms (Członkowska et al. 2018; Kalita et al. 2017).

It is known that the basal ganglia are important components of the extrapyramidal system (Bostan and Strick 2018). The main function of the basal ganglia is to control and adjust limb movements. In this study, the abnormal atrophy observed in the basal ganglia might be the cause of limb movement-related disorders in WD. It has been proved by many studies (Ala et al. 2007; Członkowska et al. 2018; Rodriguez-Castro 2015) that copper mainly deposits in the basal ganglia of WD, which are actively involved in the coordination of movement. Our findings showed that the brain atrophy was prominent in the globous pallidus and putamen. This result is consistent with previous histological and clinical studies.

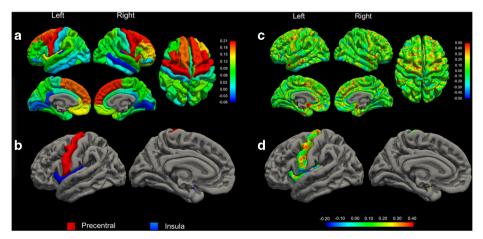


Fig. 2 Cortical thickness comparison results between WD and HC groups. Fig (a, b): Maps of the mean cortical thickness group differences at different brain lobes. Fig. (c, d): Maps of the vertex-wise cortical thickness group differences at different brain lobes. The color bar denotes the group difference of mean values (mm) at regions that had survived the FWER correction. Warmer color denotes regions where

cortical thickness is greater in HC, and cooler color denotes regions where WD patients have greater cortical thickness. Fig. (**a**, **c**): significant group differences, P < 0.05 uncorrected for multiple comparisons. Fig. (**b**, **d**): significant group differences, P < 0.0013 corrected for multiple comparisons. Fig. (**d**) shows that some areas of left precentral gyrus and left insula have decreased cortical thickness by approximately 5 mm (red)

 Table 2
 Mean cortical thickness (mm) of cortical ROIs exhibiting significant WD-vs-HC group differences

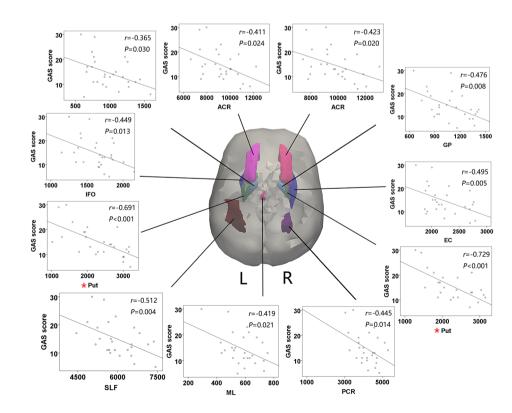
Structure	HC (mm)	WD (mm)	P values
WD < HC			
Caudal middle frontal (left)	$2.59\pm0.02$	$2.39\pm0.06$	0.0016
Medial orbitofrontal (left)	$2.63\pm0.01$	$2.49\pm0.04$	0.0251
Precentral (left)	$2.53\pm0.02$	$2.32\pm0.04$	0.0001
Superior frontal (left)	$2.87\pm0.01$	$2.69\pm0.05$	0.0193
Superior parietal (left)	$2.19\pm0.01$	$2.09\pm0.02$	0.0072
Supramarginal (left)	$2.52\pm0.02$	$2.42\pm0.03$	0.0225
Insula (left)	$3.05\pm0.02$	$\textbf{2.91} \pm \textbf{0.04}$	0.0004
Caudal middle frontal (right)	$2.57\pm0.01$	$2.38\pm0.06$	0.0300
Paracentral (right)	$2.43 \pm 0.03$	$2.34\pm0.04$	0.0350
Precentral (right)	$2.49\pm0.02$	$2.3\pm0.06$	0.0091
Precuneus (right)	$2.38\pm0.01$	$2.31\pm0.02$	0.0353
Rostral middle frontal (right)	$2.43 \pm 0.01$	$2.29\pm0.03$	0.0144
Superior frontal (right)	$2.84\pm0.01$	$2.66\pm0.04$	0.0153
Superior parietal (right)	$2.17\pm0.01$	$2.07\pm0.02$	0.0267
Insula (right)	$3.13\pm0.01$	$2.94\pm0.07$	0.0041
WD>HC			
Lingual (left)	$1.92\pm0.01$	$1.95\pm0.02$	0.0452
Lingual (right)	$1.96\pm0.01$	$1.99\pm0.02$	0.0210

Data are expressed as mean  $\pm$  standard deviation

Regular: results significant (P < 0.05) without correction for multiple comparisons; Bold: results significant with FWER correction (P < 0.0031) *HC* Healthy controls, *WD* Wilson's disease

Fig. 3 Regions where volumes significantly correlated with the GAS score in the WD group. \* Significant correlation corrected for FWER correction (P <0.0025). Volumes of the right putamen show the strongest correlation with GAS score. GAS, Global Assessment Scale for WD: L, left; R, right; ACR, anterior corona radiata; GP, globus pallidus; EC, external capsule; Put, putamen; PCR, posterior corona radiata; ML, medial lemniscus; SLF, superior longitudinal fasciculus; IFO, inferior fronto-occipital fasciculus As for the cortical abnormalities in WD, Hu et al. (Hu et al. 2017) found GM volume decreases in the middle and medial frontal gyrus, superior and middle occipital gyrus, precentral and paracentral lobule, from a VBM analysis. Stezin et al. (Stezin et al. 2016) also used VBM to reveal a significant GM volume loss in the temporal gyrus, frontal gyrus, precentral gyrus and supramarginal gyrus. VBM can only reflect cortical volume patterns but not cortical thickness patterns. Our complementary volume and thickness analyses showed GM volume decreases in the left cingulate gyrus and the bilateral superior frontal gyrus, but cortical thinning in the left precentral gyrus and the left insula. These results may suggest that volume and cortical thickness are measures at different dimensions, so the WD-related GM morphometric abnormalities have different patterns in terms of 3D volume and 2D cortical surface.

The precentral gyrus and superior frontal gyrus are related to memory processing, self-relevant processes and motor function (Guo et al. 2018; Li et al. 2013). Cortical atrophy in these regions may be associated with behavioural, cognitive and motor dysfunctions in patients with WD. Insula and cingulate gyrus are part of the limbic system, which plays an important role in emotion, behavior, motivation, self-awareness, cognitive function and interpersonal experience (Zhang et al. 2019; Caruana et al. 2018). Some patients with WD can behave as mental disorders, including anxiety, depression and excitement, etc. The mental symptoms of these patients may be related to the atrophy of the Insula and cingulate gyrus. This may also account for the difference in emotional scale scores between HC and WD.



In addition to GM atrophy, our study also found diffuse WM atrophy in WD, and the superior fronto-occipital fasciculus showed the most significant atrophy. It is known that WM lesions in WD showed obvious tissue sparsity and cavity, and the WM fibers of the internal and external capsules showed multiple demyelination (Członkowska et al. 2018; Lorincz 2018). These pathological changes may result in decreases in the volumes of the corresponding structures. Jadav et al. (Jadav et al. 2013) employed diffusion tensor imaging (DTI) to analyze patients with WD and found WM damages of the internal capsule, midbrain, pons, frontal and occipital lobes. This may suggest that WM degeneration could also present in WD.

Pearson correlation analysis showed a negative correlation between clinical score and the volumes of bilateral putamen in patients with WD, indicating that the severity of neurological symptoms may be related to nuclei of basal ganglia which are easily injured by copper deposition. The right putamen was one of the most prominently involved structures and its volume loss showed a most significant correlation with clinical scores. And thus, the right putamen volume may serve as an imaging biomarker for assessing the progression of clinical severity and the efficiency of decoppering therapy. To be noted, our study included 30 young patients with a limited sample size and a relatively short clinical course, which may explain that no correlation was found between cortical thicknesses measurements and the clinical features in patients with WD.

Previous studies were most based on VBM method, which were mainly focused on subcortical structures and cortex, but not the whole brain. In contrast, our data analyzed the whole brain volumes of 276 ROIs and cortical thicknesses of 68 cortical ROIs. ROI approach is another useful method to analyze whole brain structures. It allows for direct and accurate examination of the way that disease progression patterns take effect on specific structures of interest. In addition, VBM can only reflect cortical volume patterns, while our complementary surface-based analysis suggested that the WD-related GM morphometric abnormalities have different patterns in terms of cortical thickness. Besides methodological differences, we think, due to various reasons such as different study samples, different durations of disease and whether patients were in untreated stages, there may produce differences in different researches.

There are still several limitations of this study. First, our sample size is kind of limited. Second, our study did not classify the disease according to the disease duration and neurological symptoms due to the limited sample size. As such, our future research plans are to enlarge the sample size and update our findings.

## Conclusions

In conclusion, this study quantitatively evaluated the brain atrophy patterns of WD and demonstrated morphological abnormalities in whole brain volumes and cortical thicknesses. The identified neuroimaging abnormalities in WD can improve our understanding of the pathogenesis and progression of the disease. Moreover, certain morphometric characteristics, such as the volumes of several WM regions and the basal ganglia nuclei, maybe used as an imaging biomarker to assess disease progression.

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Author contributions Conception and study design (SYK, CJP and TXY), data collection or acquisition (SYK, ZL, HXQ, QHS and ZJ), statistical analysis (SYK, ZL), interpretation of results (SYK, ZL, HYQ, QHS, TXY and CJP), drafting the manuscript work or revising it critically for important intellectual content (SYK, ZL, TXY and CJP) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

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#### **Compliance with ethical standards**

**Conflict of interests** None of the authors have a conflict of interest to declare.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

## Appendices

#### **Subjects**

There were significant group differences in HAMD score (WD:  $10.90 \pm 5.71$ , HC:  $1.88 \pm 2.20$ ) and HAM-A score (WD:  $13.93 \pm 7.35$ , HC:  $1.32 \pm 1.70$ ) between WD and HC (P < 0.05). No significant differences were found in gender (P = 0.608,  $\chi 2$  test), age (P = 0.900, Student's t test), years of education (P = 0.270, Student's t test) nor MMSE score (P = 0.133 for Student's t test, P = 0.135 for  $\chi 2$  test) between WD and HC. For the patients with WD, the mean total disease duration time was  $43.87 \pm 19.51$  months (range: 12–84 months) and the mean GAS score was  $15.64 \pm 6.64$  (range: 5–30). A higher GAS score indicates a more severe clinical symptom. (Table 1)

full nume         full nume           is superior from-occipial fasciculus (right)         202.96±41.28           purament (right)         203.96±41.28           purament (right)         203.95±61.34           purament (right)         203.95±61.34           purament (right)         203.25±81.82.3           purament (right)         203.25±81.82.3           attracture active (right)<	Structure		НС	WD	Volume decrease rate	P values
apperior from-occipital fasciculus (right)         202.96 ± 41.28           putament (right)         444.45 ± 479.54           putament (right)         452.68 ± 480.30           seperior fromo-occipital fasciculus (reft)         252.66 ± 480.30           seperior fromo-occipital fasciculus (reft)         257.68 ± 480.30           seperior fromo-occipital fasciculus (reft)         257.68 ± 480.30           seperior fromo-occipital fasciculus (reft)         257.68 ± 189.00           seperior fromo-occipital fasciculus (reft)         257.58 ± 55.58           sobia palidas (reft)         257.58 ± 55.58           sobia palidas (reft)         257.58 ± 55.58           sobia palidas (reft)         257.58 ± 55.58           audate molens (right)         202.58 ± 18.23           autoclas accumbens (right)         202.58 ± 18.24           autoclas accumbens (right)         202.54 ± 18.24           autoclas accumbens (right)         202.54 ± 18.24      <	Abbreviation	full name				
L         202.96±4128           Purprior fronto-occipital fisciculus (right)         202.96±4128           Putament (eff)         464.45±4755           Putament (eff)         426.68±40.30           Strend coprise frento-occipital fisciculus (tel)         425.68±40.30           R         substantia nigra (tef)         425.68±46.03           R         substantia nigra (tef)         427.64±45.60           R         substantia nigra (tef)         527.54±45.60           R         substantia nigra (tef)         527.54±6.138           L         cutates uccurbers (tigh)         527.54±6.138           L         cutates uccurbers (tigh)         527.54±7.53           autoter costing natic (tigh)         527.54±18.4           autoter costing natic (tigh)         527.54±18.54           autoter costing natic (tigh)         527.54±18.55           autoter costing natec (tigh)<	WD <hc< td=""><td></td><td></td><td></td><td></td><td></td></hc<>					
L         test state         4644.45±79.54           Dutament (right)         state         4644.45±79.54           L         superior from coccipital fasciculus (left)         365.64±40.30           R         superior from coccipital fasciculus (left)         365.64±40.30           R         substantia ign (left)         358.70±43.53           R         substantia ign (left)         358.74±40.30           R         substantia ign (left)         350.54±40.30           R         substantia ign (left)         350.54±18.24           R         substantia ign (left)         350.54±18.24           R         substantia ign (left)         350.54±	SFO R	superior fronto-occipital fasciculus (right)	$202.96 \pm 41.28$	$94.81 \pm 36.41$	53.29%	<0.0001
L     superior field)     255.88+480.30       R     superior field)     255.88+58.35       R     superior field)     255.88+58.50       R     superior field)     255.88+55.60       R     superior field)     255.88+55.60       R     superior field)     255.88+55.60       R     superior field)     255.88+40.30       R     substantia ingr (fet)     255.88+40.30       R     substantia ingr (fet)     255.88+40.90       R     nucleus accumbers (figh)     255.88+40.90       R     nucleus accumbers (figh)     350.28+40.90       R     nucleus accumbers (figh)     350.28+40.90       R     nucleus accumbers (figh)     350.28+40.90       alWM ACC     automotes (figh)     350.28+40.90       alWM ACC     subortical white matter of the subgenul anterior     352.54+40.90       naterior criguitus cortix (figh)     350.28+18.3.2       automotes (figh)     350.28+18.3.2       automotes (figh)     350.28+18.3.4	Put R	putamen (right)	$4644.45 \pm 479.54$	$2393.89 \pm 637.93$	48.32%	<0.0001
$ \begin{array}{cccc} & \mbox{cremal capsule in the clastrum (right)} & \mbox{cremal capsule cortex (right)} & \mbox{cremal capsule cortex (right)} & \mbox{cremal capsule (right)} & \mbox{cremal capsule cortex (right)} & \mbox{cremal capsule (right)} & \mbox{cremal capsule (right)} & \mbox{cremal capsule cortex (right)} & \mbox{cremal capsule (right)} & cremal capsule (right$	Put L	putamen (left)	$4526.80 \pm 480.30$	$2378.78 \pm 750.87$	47.15%	<0.0001
$ \begin{array}{ccccccc} \label{eq:constraint agent (eft) \\ \mbox{alpharmin agent (eft) } \mbox{alpharmin adent (eft) } alpharmin a$	SFO L	superior fronto-occipital fasciculus (left)	$297.00 \pm 54.03$	$164.56 \pm 60.18$	44.59%	<0.0001
L       substantia nigra (teth)       355,584,550         R       externatia nigra (right)       325,584,550         R       globus palliotis (rth)       325,584,550         R       globus palliotis (rth)       325,584,550         R       externation nigra (right)       325,584,550         R       externation nigra (right)       325,584,550         R       reducter accumbers (right)       325,584,8500         R       reducter accumbers (right)       325,584,8500         R       reducter nucleus (right)       325,584,8500         R       reducter nucleus (right)       320,284,409,966         R       reducter nucleus (right)       312,424,3585         autwork reduction white matter of the subgenual anterior       312,424,358         autwork reduction white matter of the subgenual anterior       312,544,823         autwork reduction white matter of the subgenual anterior       312,544,823         autwork reduction white matter of the subgenual anterior       312,424,358         autwork reduction white matter of the subgenual anterior       312,424,358         autwork reduction white matter of the subgenual anterior       312,424,358         autwork reduction white matter of the subgenual anterior       312,424,353         auterior cingulate cortex (right) <t< td=""><td>ECCL L</td><td>external capsule in the claustrum (left)</td><td><math>484.79 \pm 52.73</math></td><td><math>276.93 \pm 72.34</math></td><td>42.88%</td><td>&lt;0.0001</td></t<>	ECCL L	external capsule in the claustrum (left)	$484.79 \pm 52.73$	$276.93 \pm 72.34$	42.88%	<0.0001
R         external capsule in the claastrum (right)         552,588 ±55.58           R         gobus palidus (eft)         557,864 ±80.00           L         L         external capsule (right)         557,864 ±80.00           R         admucleus accumbers (left)         268,38 ±45.00         268,38 ±45.00           R         admucleus accumbers (left)         260,55 ± 40.96         268,38 ±45.00           R         admucleus accumbers (right)         3502,58 ± 40.96         268,38 ±45.00           R         admucleus accumbers (right)         3502,58 ± 40.96         268,38 ±45.06           aution cacks accumbers (right)         3502,58 ± 40.96         3512,42 ± 35.85           aution cacks accumbers (right)         353,54 ± 10.50         353,54 ± 10.50           aution cacks accumbers (right)         353,54 ± 10.50         353,54 ± 10.53           aution cacks accumbers (right)         353,54 ± 10.53         353,54 ± 10.53           aution cacks (right)         200,25 ± 31.11         353,54 ± 10.53           aution cacks (right)         353,54 ± 10.53         353,54 ± 10.53           controspinal tract(right)         201,25,49         203,17 ± 12.24           controspinal tract(right)         203,54 ± 203,37         204,64 ± 12.77           condito mucleus (right)         201,54 ± 203,37<	Snigra L	substantia nigra (left)	$398.70 \pm 34.50$	$213.94 \pm 78.05$	38.24%	<0.0001
R         globus palidus (eft)         1537.84 ± 189.00           L         nucleus accumbers (eft)         263.74 ± 41.90           L         nucleus accumbers (right)         263.74 ± 41.90           R         nucleus accumbers (right)         263.74 ± 40.90           R         nucleus accumbers (right)         350.25 ± 41.90           R         nucleus accumbers (right)         350.25 ± 41.90           R         nucleus accumbers (right)         351.24 ± 82.64           atWM ACC R         subcortical white matter of the subgenual anterior cingulate cortex (right)         312.42 ± 8.82.3           atWM ACC L         subcortical white matter of the subgenual anterior         312.42 ± 8.82.3           atward cortical white matter of the subgenual anterior         312.42 ± 8.8.23           atward cortical white matter of the subgenual anterior         312.42 ± 8.8.23           atward cortical white matter of the subgenual anterior         312.42 ± 8.8.23           attword cortical white matter of the subgenual anterior         200.25 ± 11.11           conticospinal tract(right)         312.42 ± 8.8.23           attword cortical white matter of the subgenual anterior         200.25 ± 11.11           conticospinal tract(right)         207.25 ± 24.97.54           attword cortical white matter of the subgenual anterior         207.25 ± 24.97.54 </td <td>ECCL R</td> <td>external capsule in the claustrum (right)</td> <td><math>525.58 \pm 55.58</math></td> <td><math>328.37 \pm 65.41</math></td> <td>37.52%</td> <td>&lt;0.0001</td>	ECCL R	external capsule in the claustrum (right)	$525.58 \pm 55.58$	$328.37 \pm 65.41$	37.52%	<0.0001
Rauthorns Lsubstantia ngra (right) $268.38 \pm 45.00$ cumbens Lnucleus accumbers (left) $700.75 \pm 60.38$ Rnucleus accumbers (right) $350.258 \pm 40.996$ Rnucleus accumbers (right) $312.42 \pm 5.88$ autWM ACC RautWM ACC I $312.54 \pm 82.64$ autWM ACC Lsubcortical white matter of the subgenual $312.54 \pm 82.64$ autWM ACC Rautwork (right) $312.54 \pm 82.64$ autWM ACC Lsubcortical white matter of the subgenual $312.52 \pm 18.34$ autwork C Rautwork (right) $312.52 \pm 82.64$ autwork C Rautor activation (right) $325.54 \pm 20.37$ autor c rossing tract (right) $207.52 \pm 61.82$ conduct ortex (right) $297.52 \pm 81.82$ controssymal tractor (right) $297.52 \pm 81.82$ controssymal tractor (right) $297.52 \pm 18.25$ controssymal tractor (right) $297.52 \pm 18.25$ controssymal tractor (right) $297.52 \pm 18.26$ controssymal tractor (right) $297.52 \pm 18.25$ controssymal tractor (right) $297.29 \pm 102.35$ superior corona radian (right) $297.29 \pm 102.35$ medial lemniscus (right) $297.29 \pm 102.35$ corticospinal tractor (right) $297.29 \pm 29.71$ corticospinal tractor (right) $297.29 \pm 102.35$ corticospinal tractor (right) $297.29 \pm 29.21$ corticospinal tractor (right)	GP L	globus pallidus (left)	$1527.86 \pm 189.00$	$987.11 \pm 289.23$	37.13%	<0.0001
aumbens L     mucleus accumbers (left)     700.75 ± 60.38       red mucleus (right)     390.2.85± 40.96       R     mucleus accumbers (right)     390.2.85± 40.96       alWM ACC R     globs pillulas (right)     312.42± 35.85       aulWM ACC R     globs pillulas (right)     312.42± 35.85       aulWM ACC R     globs pillulas (right)     350.2.55± 80.264       aulWM ACC I     suboritical white matter of the subgenual     352.5± 82.34       aulWM ACC I     suboritical white matter of the subgenual     352.5± 82.34       aulWM ACC I     suboritical white matter of the subgenual     373.5± 81.82       autoric original tract(right)     373.5± 82.34       postime crossing tract (right)     200.25± 31.11       cingulate cortex (left)     200.25± 31.11       cingulate cortex (left)     200.25± 41.05.35       posterior limb of internal capsule (right)     207.55± 82.04       superior corona radiata (left)     155.128       auterior corona radiata (left)     12.54.177753       auterior corona radiata (right)     202.54± 110.753       medial lemmiscus (left)     13.192.63± 1425.59       auterior corona radiata (right)     227.29± 249.74       auterior corona radiata (left)     13.192.63± 1425.53       auterior corona radiata (left)     229.729± 249.71       medial lemmiscus (left)     127.7	Snigra R	substantia nigra (right)	$268.38 \pm 45.60$	$185.20 \pm 45.35$	35.09%	<0.0001
L chadae nucleus (right) 289.14 41.90 caudate nucleus (right) 350.58 ± 409.96 red nucleus (right) 350.58 ± 409.96 aulWM ACC R subtranter of the subgenual anterior cingulate cortex (right) 352.5 ± 18.34 anterior cingulate cortex (right) 352.5 ± 18.34 anterior cingulate cortex (right) 352.5 ± 18.34 anterior cingulate cortex (right) 200.25 ± 11.1 cingulate cortex (right) 200.25 ± 14.25.59 posterior inter of internal capsule (right) 200.25 ± 10.53.43 corticospinal tract(right) 15.428.67 ± 1707.53 auperior corona radiata (right) 200.25 ± 10.31 anterior corona radiata (right) 200.25 ± 10.31 cortex (right) 200.125.81 ± 105.26 auperior corona radiata (right) 200.26 ± 1.25.59 cortex areas and the corona radiata (right) 200.26 ± 1.277.73 auperior corona radiata (right) 200.26 ± 1.277.73 cortex areas areas (right) 200.29 ± 2.26.25 anterior radia (right) 200.200.25 anterior	NucAccumbens L	nucleus accumbens (left)	$700.75 \pm 60.38$	$457.89 \pm 116.64$	34.66%	<0.0001
R       cadadate nucleus (right)       5502.58 ± 409.96         authons R       nucleus scrubbens (right)       515.258 ± 48.823         authons R       nucleus scrubbens (right)       515.34 ± 82.64         alWM ACC R       subcortical white matter of the subgenual anterior       93.25 ± 18.34         alWM ACC L       subcortical white matter of the subgenual anterior       93.25 ± 18.34         anterior cingulate cortex (right)       93.25 ± 18.34       93.25 ± 18.34         anterior corsona radiat tract(fight)       200.25 ± 31.11       200.25 ± 31.11         contiduation of internal capsule (right)       200.25 ± 18.25       200.4 ± 995.55         contiduation of internal capsule (right)       200.25 ± 18.24       209.37         posterior limb of internal capsule (right)       200.25 ± 107.35       297.35 ± 269.37         corticospinal tract(right)       1455.58 ± 165.3.43       297.35 ± 426.71707.53         superior corsona radiat (right)       297.32 ± 249.74       297.32 ± 249.74         nedial lemniscus (right)       297.3 ± 249.74       297.35 ± 249.74         nedial lemniscus (right)       297.25 ± 249.74       297.52 ± 249.74         nedial lemniscus (right)       297.54 ± 107.73       297.54 ± 127.73         nedial lemniscus (right)       297.54 ± 149.74       297.54 ± 149.74	RedNc L	red nucleus (left)	$289.14 \pm 41.90$	$197.78 \pm 27.58$	34.46%	<0.0001
R         red nucleus (right)         312.42 ± 35.65           antwortical white matter of the subgenual antwortical white matter of the subgenual conticosphilal tract(right)         312.42 ± 38.23           alWM ACC L         conticosphila tract(right)         200.25 ± 31.11           conticosphila tract(right)         200.25 ± 31.11         200.25 ± 31.23           conticosphila tract(right)         235.35 ± 999.53         248.90.44 ± 399.55           conticosphila tract(right)         237.29 ± 24.97         349.04 ± 397.73           condial lemniscus (left)         23.97.29 ± 24.97         342.6.92 ± 217.33           controsphila tractorized (right)         23.97.29 ± 24.97         349.04 ± 1277.73           medial lemniscus (left)         23.97.29 ± 24.97         34.92.55           controsphila tractorized (right)         23.96.96 ± 217.33         24.95.26           controsphila tractoricoron aradiata (right)         29.65.04 ± 198.77<	Caud R	caudate nucleus (right)	$3502.58 \pm 409.96$	$2374.7 \pm 433.66$	32.20%	<0.0001
autwork R     nucleus accumbens (right)     815.54 ± 82.64       autwm ACC R     globus palifier (right)     815.54 ± 82.23       autwm ACC L     autorritical white matter of the subgenual amerior     93.25 ± 18.3.23       autwm ACC L     autocritical white matter of the subgenual amerior     93.25 ± 18.2.3       autwm ACC L     autocritical white matter of the subgenual amerior     93.25 ± 18.2.3       autwm ACC L     autocritical white matter of the subgenual amerior     200.25 ± 31.11       autocron cargo right     207.25 ± 18.2.3       pointine correx (right)     349.04 ± 90.5.55       corticosprinal tract(right)     349.04 ± 90.5.55       superior corona radian (right)     1453.584 ± 1707.53       superior corona radian (right)     12.81.7 ± 124.26       superior corona radian (right)     12.927.29 ± 49.74       naterior corona radian (right)     297.29 ± 49.74       naterior corona radian (right)     297.29 ± 49.74       naterior corona radian (right)     297.29 ± 207.39       naterior corona radian (right)     296.9 ± 1425.59       naterior corona radian (right)     297.29 ± 207.31       naterior corona radian (right)     297.29 ± 207.39       naterior rinno of internal capsule (reft)     2.397.45 ± 127.773       naterior rinno of internal capsule (reft)     2.397.29 ± 207.39       naterior rinno of internal capsule (reft) <td>RedNc R</td> <td>red nucleus (right)</td> <td><math>312.42 \pm 35.85</math></td> <td><math>221.70 \pm 62.35</math></td> <td>31.89%</td> <td>&lt;0.0001</td>	RedNc R	red nucleus (right)	$312.42 \pm 35.85$	$221.70 \pm 62.35$	31.89%	<0.0001
alWM ACC R     globus pallidus (right)     1578.98 ± 182.23       alWM ACC L     subcortical white matter of the subgenual anterior     9.3.25 ± 18.2.3       alWM ACC L     subcortical white matter of the subgenual anterior     9.3.25 ± 18.2.3       anterior cingulate cortex (left)     9.3.25 ± 18.2.2       pointine crossing tract (right)     200.25 ± 31.11       cingulate cortex (left)     200.25 ± 31.11       pointine crossing tract (right)     1453.58 ± 195.59       posterior limb of internal capsule (right)     2973.54 ± 269.37       conticospinal tract(right)     1453.54       conticospinal tract(right)     2973.54 ± 126.53       superior corona radiata (right)     2973.54 ± 124.56       conticospinal tract(right)     298.21 ± 23.591       medial lemniscus (left)     15.42.867 ± 170.753       medial lemniscus (left)     13.192.63 ± 1435.591       metrior corona radiata (right)     296.24 ± 23.591       anterior corona radiata (right)     296.24 ± 23.591       metrior corona radiata (right)     296.36 ± 11.31       metrior corona radiata (right)     296.96 ± 2117.33       metrior corona radiata (right)     296.96 ± 2117.33       external capsule (right)     296.36 ± 18.57       metrior inmo of internal capsule (right)     296.36 ± 18.27773       materior inmo of internal capsule (right)     296.96 ± 117.33 <td>NucAccumbens R</td> <td>nucleus accumbens (right)</td> <td><math>815.54 \pm 82.64</math></td> <td><math>559.89 \pm 123.41</math></td> <td>31.35%</td> <td>&lt;0.0001</td>	NucAccumbens R	nucleus accumbens (right)	$815.54 \pm 82.64$	$559.89 \pm 123.41$	31.35%	<0.0001
alWM ACC R subcortical white matter of the subgenual anterior anterior cingulate cortex (right) abcortical white matter of the subgenual anterior abcortical white matter of the subgenual anterior anterior cingulate cortex (right) abcortical white matter of the subgenual anterior anterior cingulate cortex (right) as sec. 50 ± 81.82 corticospinal tract(fet) 113.35.50 ± 81.82 corticospinal tract(fet) 143.55 superior corton radiate (right) 2973.54 ± 269.37 caudate muletas (fet) 2974.54 ± 193.10 caternal capsule (fet) 2974.54 ± 193.11 caternal capsule (fet) 296.96 ± 21773 medial lemitors (fet) 296.96 ± 21733 carebral peduncle (fet) 296.96 ± 21733 carebral peduncle (fet) 296.96 ± 21733 carebral reduce (fet) 1277.96 ± 155.84 medial lemitors (fet) 296.96 ± 21733 carebral reduce (fet) 193.10 ± 166.92 ± 185.25 medial muletar (fet) 296.96 ± 21733 carebral reduce (fet) 193.10 ± 167.96 ± 155.84 metricor limb of internal capsule (fet) 296.96 ± 21733 carebral reduce (fet) 202.35 metricor lemitor (fet) 296.95 ± 207.39 millota in (fet) 297.35 metricor limb of internal capsule (fet) 202.35 metricor limb of 2	GP R	globus pallidus (right)	$1578.98 \pm 188.23$	$1096.85\pm233.21$	30.59%	<0.0001
alWM ACC Lanterior cingulate cortex (right) $200.25 \pm 31.11$ auterior cingulate cortex (left) $582.50 \pm 81.82$ pontine crossing tract (ight) $582.50 \pm 81.82$ pontine crossing tract (ight) $582.50 \pm 81.82$ pontine crossing tract (ight) $2937.54 \pm 269.37$ posterior limb of internal capsule (right) $2937.54 \pm 269.37$ posterior corona radiata (right) $2937.54 \pm 269.37$ corticospinal tract(ight) $2937.54 \pm 269.37$ superior corona radiata (left) $2937.29 \pm 292.91$ superior corona radiata (left) $2937.29 \pm 242.74$ posterior limb of internal capsule (left) $2937.20 \pm 242.74$ needial lemniscus (left) $2937.20 \pm 242.74$ needial lemniscus (left) $2937.20 \pm 242.74$ needial lemniscus (right) $2980.24 \pm 110.31$ cerebral lemniscus (right) $2937.20 \pm 242.73$ needial lemniscus (right) $2936.21 \pm 235.91$ needial lemniscus (right) $2936.21 \pm 235.91$ needial lemniscus (right) $2936.92 \pm 207.73$ needial lemniscus (right) $2936.92 \pm 207.33$ needial lemniscus (right) $297.29 \pm 207.13$ needial lemniscus (right) $2936.92 \pm 207.39$ needrain Lnaterior limb of internal capsule (right)neotrain Rbasal forebrain (left)neotrain Rnaterior limb of internal capsule (right)neotrain Rnaterior limb of internal capsule (right)numbrain (right) $2137.29 \pm 207.13$ numbrain (right) $2137.29 \pm 207.39$ numbrain (right) $2137.29 \pm 207.39$ <	subgenualWM ACC R	subcortical white matter of the subgenual	$93.25 \pm 18.34$	$64.78 \pm 15.03$	30.53%	<0.0001
adWM ACC LadWM ACC Lcingulate ordex (left) $200.25 \pm 31.11$ cingulate cortex (left)pontine crossing tract (right) $582.50 \pm 81.82$ pontine crossing tract (right) $582.50 \pm 81.82$ pontine crossing tract (right) $582.50 \pm 81.82$ posterior limb of internal capsule (right) $2973.54 \pm 269.37$ superior corona radiata (right) $1453.84 \pm 90.55$ superior corona radiata (right) $15.70.83 \pm 1653.43$ concospinal tract(right) $15.70.83 \pm 1653.43$ concospinal tract(right) $15.42.867 \pm 1707.53$ medial lemniscus (left) $2973.29 \pm 292.91$ posterior limb of internal capsule (left) $2237.29 \pm 249.74$ anterior corona radiata (right) $13.192.663 \pm 1425.59$ external capsule (left) $2297.46 \pm 1277.73$ medial lemniscus (left) $298.21 \pm 235.91$ medial lemniscus (right) $298.21 \pm 235.91$ medial lemniscus (right) $296.24 \pm 119.31$ cerebral peduncle (left) $13.102.69 \pm 1277.73$ medial lemniscus (right) $298.21 \pm 235.91$ medial lemniscus (right) $298.21 \pm 235.91$ medial lemniscus (right) $298.21 \pm 235.91$ medial lemniscus (right) $297.42 \pm 119.31$ external capsule (right) $13.102.64 \pm 1277.73$ medial lemniscus (right) $297.92 \pm 207.18$ medial lemniscus (right) $297.92 \pm 207.18$ medial lemniscus (right) $298.21 \pm 238.72$ medial lemniscus (right) $297.92 \pm 207.18$ medial lemniscus (right) $297.92 \pm 207.38$ medial lemniscus (right)<		anterior cingulate cortex (right)				
cingulate cortex (left) $82.50 \pm 81.82$ pontine crossing tract (right) $582.50 \pm 81.82$ pontine crossing tract (right) $582.50 \pm 81.82$ controspinal tract(rt) $582.50 \pm 81.82$ controspinal tract(rt) $582.50 \pm 81.82$ posterior corona radiata (right) $2773.54 \pm 269.37$ superior corona radiata (right) $273.54 \pm 269.37$ conticospinal tract(right) $15.170.83 \pm 1653.43$ conticospinal tract(right) $12.58.17 \pm 124.26$ superior corona radiata (right) $297.29 \pm 49.74$ medial lemniscus (left) $297.29 \pm 49.74$ metrior corona radiata (left) $297.29 \pm 49.74$ metrior corona radiata (left) $297.29 \pm 49.74$ metrior corona radiata (left) $297.42 \pm 119.31$ medial lemniscus (right) $298.21 \pm 235.91$ medial lemniscus (right) $296.21 \pm 235.91$ medial lemniscus (right) $296.24 \pm 119.31$ webrain Lmedial lemniscus (right)setternal capsule (left) $176.94 \pm 198.72$ formix/stria terminalis (left) $1787.92 \pm 207.33$ webrain Lmedial lemniscus (right)setternal capsule (right) $2143.29 \pm 207.33$ medial forebrain (right) $2143.29 \pm 207.33$ metrior limb of internal capsule (right) $2143.29 \pm 207.33$ metrior limb of internal capsule (right) $2143.29 \pm 207.33$ metrior limb of internal capsule (right) $2143.29 \pm 207.33$ metrior limb of internal capsule (right) $2143.29 \pm 207.33$ metrior limb of internal capsule (right) $2143.29 \pm 207.33$ mi	subgenualWM ACC L	subcortical white matter of the subgenual anterior	$200.25 \pm 31.11$	$142.11 \pm 29.62$	29.03%	<0.0001
pontune crossing tract (right) $882.50 \pm 81.82$ corticospinal tract(left) $1453.58 \pm 195.59$ posterior line nucleus (fr) $1453.58 \pm 195.59$ posterior corona radiata (right) $2973.54 \pm 269.37$ corticospinal tract(right) $2973.54 \pm 269.37$ superior corona radiata (right) $2973.54 \pm 269.37$ corticospinal tract(right) $2973.54 \pm 269.37$ superior corona radiata (right) $15,428.67 \pm 1707.53$ superior corona radiata (right) $15,428.67 \pm 1707.53$ nedial lemniscus (left) $13,192.65 \pm 1425.59$ anterior corona radiata (right) $2977.29 \pm 249.74$ naterior corona radiata (right) $2977.29 \pm 249.74$ anterior corona radiata (right) $2977.29 \pm 249.74$ naterior corona radiata (right) $2986.21 \pm 235.91$ anterior corona radiata (right) $2986.92 \pm 217.73$ cerebral peduncle (right) $12,397.46 \pm 1277.73$ cerebral peduncle (right) $12,397.46 \pm 1277.73$ cerebral peduncle (right) $12,397.46 \pm 1277.73$ cerebral peduncle (right) $298.42 \pm 207.39$ anterior corona radiata (right) $2143.29 \pm 207.39$ anterior limb of internal capsule (right) $2143.29 \pm 2277.39$ anterior limb of internal capsule (right) $2146.42 \pm 248.78$ anterior limb of internal capsule (right) $2143.29 \pm 2277.39$ anterior limb of internal capsule (right) $2143.29 \pm 2277.39$ anterior limb of internal capsule (right) $2143.29 \pm 2277.39$ anterior limb of internal capsule (right) $2143.29 \pm 2277.39$ in Lmidbrain (ri		cingulate cortex (left)				0
$\cdot$	PCLR	pontine crossing tract (right)	$582.50 \pm 81.82$	$416.59 \pm 81.79$	28.48%	<0.001
$\begin{array}{llllllllllllllllllllllllllllllllllll$	CSTL	corticospinal tract(left)	$1453.58 \pm 195.59$	$1044.70 \pm 222.37$	28.13%	0.0001
caudate nucleus (lett) $3489,04 \pm 399,55$ superior corona radiata (right) $5,170.83 \pm 1653.43$ corticospinal tract(right) $5,170.83 \pm 1653.43$ superior corona radiata (left) $15,428.67 \pm 1707.53$ superior corona radiata (left) $15,428.67 \pm 1707.53$ medial lemniscus (left) $789,42 \pm 92.91$ posterior limb of internal capsule (left) $2986.21 \pm 235.91$ anterior corona radiata (left) $2986.21 \pm 235.91$ anterior corona radiata (left) $2986.21 \pm 235.91$ anterior corona radiata (left) $296.96 \pm 217.33$ anterior corona radiata (left) $12.397.46 \pm 1277.73$ anterior limb of internal capsule (right) $12.397.46 \pm 1277.73$ cerebral peduncle (left) $12.397.46 \pm 12.77.73$ cerebral peduncle (left) $1786.19 \pm 128.52$ to midbrain Lanterior limb of internal capsule (left)basal forebrain (left) $1785.13 \pm 155.22$ in Lmaterior limb of internal capsule (left)in Rpasal forebrain (left) $2143.29 \pm 207.18$ in Rmidbrain (left) $2143.29 \pm 207.18$ in Rmidbrain (left) $2143.29 \pm 207.39$ in Rmidbrain (left) $2143.29 \pm 192.35$ postor corona radiata (left) $200.65.47.202.48$ <td>PLICR</td> <td>posterior limb of internal capsule (right)</td> <td><math>2973.54 \pm 269.37</math></td> <td><math>2148.11 \pm 406.86</math></td> <td>27.76%</td> <td>&lt;0.0001</td>	PLICR	posterior limb of internal capsule (right)	$2973.54 \pm 269.37$	$2148.11 \pm 406.86$	27.76%	<0.0001
superior corona radiata (right) $15,170.83 \pm 1653.43$ superior corona radiata (right) $1258.17 \pm 124.26$ superior corona radiata (left) $15,428.67 \pm 1707.53$ medial lemniscus (left) $2927.29 \pm 292.91$ posterior limb of internal capsule (left) $297.29 \pm 249.74$ anterior corona radiata (left) $297.62 \pm 1425.59$ anterior corona radiata (left) $2986.21 \pm 235.91$ anterior corona radiata (left) $2986.21 \pm 235.91$ anterior corona radiata (left) $2962.42 \pm 149.31$ anterior corona radiata (left) $2969.96 \pm 217.33$ cerebral lemniscus (right) $2069.96 \pm 217.33$ cerebral peduncle (left) $167.96 \pm 1277.73$ medial lemniscus (right) $2969.96 \pm 217.33$ cerebral peduncle (right) $197.6.94 \pm 198.72$ formix/stria terminalis (left) $1785.13 \pm 155.22$ tractoral limb of internal capsule (right) $164.08 \pm 131.08$ basal forebrain (left) $1785.13 \pm 155.22$ in Lmaterior limb of internal capsule (right) $2143.29 \pm 207.18$ in Lmidbrain (right) $2143.29 \pm 207.18$ in Rmidbrain (right) $2143.29 \pm 207.18$ in Rmidbrain (right) $2143.29 \pm 207.18$ in Rmodiaran (right) $2143.29 \pm 207.39$ in Rmidbrain (right) $2143.29 \pm 207.39$ in Rmodibrain (right) $2143.29 \pm 207.39$ <td>Caud L</td> <td>caudate nucleus (left)</td> <td><math>3489.04 \pm 399.55</math></td> <td><math>2529.52 \pm 778.43</math></td> <td>27.50%</td> <td>&lt;0.0001</td>	Caud L	caudate nucleus (left)	$3489.04 \pm 399.55$	$2529.52 \pm 778.43$	27.50%	<0.0001
corticospinal tract(right)1258.17 ± 124.26superior corona radiata (left) $15,428.67 \pm 1707.53$ medial lemniscus (left) $2927.29 \pm 249.74$ posterior limb of internal capsule (left) $297.29 \pm 249.74$ anterior corona radiata (right) $296.21 \pm 23.59$ external capsule (left) $296.21 \pm 23.59$ anterior corona radiata (left) $296.21 \pm 23.59$ anterior corona radiata (left) $296.24 \pm 109.31$ anterior corona radiata (left) $2069.96 \pm 217.73$ medial lemniscus (right) $2069.96 \pm 217.73$ external capsule (left) $1785.92 \pm 188.51$ cerebral peduncle (left) $176.04 \pm 198.72$ for internal capsule (right) $176.04 \pm 198.72$ for internal capsule (right) $1787.92 \pm 248.78$ basal forebrain (left) $1785.13 \pm 155.22$ anterior limb of internal capsule (right) $2143.29 \pm 207.18$ in Lmidbrain (right) $2143.29 \pm 207.18$ in Lmidbrain (right) $2143.29 \pm 122.35$ in Rposterior corona radiata (right) $2143.29 \pm 122.35$ posterior limb of internal capsule (left) $2143.29 \pm 122.35$ fin Lmidbrain (right) $2143.29 \pm 122.35$ fin Rposterior corona radiata (right) $2006.32 \pm 207.39$ fin Rposterior corona radiata (right) $2143.29 \pm 122.35$ fin Rposterior limb of internal capsule (left) $200.52 \pm 720.25$ fin Rposterior corona radiata (right) $200.53 \pm 207.39$ fin Rposterior limb of $53 \pm 207.39$ fin R </td <td>SCR R</td> <td>superior corona radiata (right)</td> <td><math>15,170.83 \pm 1653.43</math></td> <td><math>11,036.81 \pm 1558.27</math></td> <td>27.25%</td> <td>&lt;0.0001</td>	SCR R	superior corona radiata (right)	$15,170.83 \pm 1653.43$	$11,036.81 \pm 1558.27$	27.25%	<0.0001
Csuperior corona radiata (left) $15,428.67\pm170.53$ Lnedial lemniscus (left) $15,428.67\pm170.53$ Lposterior limb of internal capsule (left) $2927.29\pm249.74$ Ranterior corona radiata (nght) $2927.29\pm249.74$ Lanterior corona radiata (left) $2956.21\pm25.59$ Lanterior corona radiata (left) $296.24\pm1277.73$ needial lemniscus (right) $2960.96\pm217.33$ cerebral peduncle (right) $962.96\pm217.33$ cerebral peduncle (right) $962.96\pm217.33$ cerebral peduncle (right) $1785.13\pm10.8$ Forebrain L $2969.96\pm217.33$ anterior limb of internal capsule (right) $176.94\pm193.72$ for brain L $2969.96\pm217.33$ anterior limb of internal capsule (right) $1785.13\pm15.22$ Rbasal forebrain (left) $1785.13\pm15.522$ Ranterior limb of internal capsule (right) $2143.29\pm192.35$ anterior limb of internal capsule (right) $2348.92\pm207.39$ anterior limb of internal capsule (right) $2143.29\pm192.35$ anterior limb of internal capsule (right) $2143.29\pm192.35$ anterior limb of internal capsule (right) $2000.63\pm720.25$ anterior limb of internal capsule (right) $2143.29\pm192.35$ anterior limb of internal capsule (right) $2000.6$	CSTR	corticospinal tract(right)	$1258.17 \pm 124.26$	$915.96 \pm 182.90$	27.20%	<0.0001
Lmedial lemnacus (left) $789.42 \pm 92.91$ Ranterior corona radiata (right) $2927.29 \pm 249.74$ Ranterior corona radiata (right) $2927.29 \pm 249.74$ Lanterior corona radiata (left) $2926.51 \pm 235.91$ Lanterior corona radiata (left) $2986.21 \pm 235.91$ Lanterior corona radiata (left) $2969.6 \pm 217.73$ nedial lemniscus (right) $962.42 \pm 119.31$ external capsule (right) $965.42 \pm 119.31$ everbral peduncle (right) $1976.04 \pm 198.72$ Cerebral peduncle (right) $1976.04 \pm 198.72$ Rbasal forebrain (left) $1785.13 \pm 155.22$ Ranterior limb of internal capsule (right) $1785.13 \pm 155.22$ Ranterior limb of internal capsule (right) $2143.29 \pm 207.18$ Lanterior limb of internal capsule (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (right) $2143.29 \pm 207.39$ anterior limb of internal capsule (right) $2143.29 \pm 207.39$ anterior limb of internal capsule (right) $2143.29 \pm 102.35$ anterior limb of internal capsule (right) $2000.63 \pm 207.39$ anterior limb of internal capsule (right) $2143.29 \pm 207.39$ anterior limb of internal capsule (right) $2143.29 \pm 207.39$ anterior limb of internal capsule (right) $2143.29 \pm 207.39$ and for homologinal (right) $2143.29 \pm 207.39$ and for homologinal (right) $2143$	SCRL	superior corona radiata (left)	$15,428.67 \pm 1707.53$	$11,259.37 \pm 1718.77$	27.02%	<0.0001
L posterior limb of internal capsule (left) $2927.29 \pm 249.74$ R anterior corona radiata (left) $13.192.63 \pm 1425.59$ anterior corona radiata (left) $13.192.63 \pm 1425.59$ external capsule (left) $12.397.46 \pm 1277.73$ medial lemniscus (right) $96.2.42 \pm 119.31$ external capsule (left) $12.969.96 \pm 217.33$ reternal capsule (left) $1976.04 \pm 198.72$ formix/stria terminalis (left) $1976.04 \pm 198.72$ formix/stria terminalis (left) $1785.13 \pm 155.22$ R basal forebrain (left) $1785.13 \pm 155.22$ R anterior limb of internal capsule (right) $2149.42 \pm 248.78$ forebrain L michon in (left) $1785.13 \pm 155.22$ R anterior limb of internal capsule (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (right) $2313.2248.72 \pm 2152.92 \pm 207.18$ anterior limb of internal capsule (right) $2313.92 \pm 207.18$ anterior limb of internal capsule (right) $2313.92 \pm 207.39 \pm 155.22 \pm 155.$	MLL	medial lemniscus (left)	$789.42 \pm 92.91$	$576.70 \pm 107.65$	26.95%	<0.0001
Ranterior corona radiata (right) $13,192.63 \pm 1425.59$ Lanterior corona radiata (right) $2986.21 \pm 235.91$ Lanterior corona radiata (left) $12,397.46 \pm 1277.73$ unction corona radiata (left) $12,397.46 \pm 1277.73$ anterior corona radiata (left) $962.42 \pm 119.31$ external capsule (ight) $962.42 \pm 119.31$ external capsule (ight) $1976.04 \pm 198.72$ tformix/stria terminalis (left) $1976.04 \pm 198.72$ tbasal forebrain (left) $1976.04 \pm 198.72$ formix/stria terminalis (left) $1785.13 \pm 155.22$ Ranterior limb of internal capsule (right) $1785.13 \pm 155.22$ Ranterior limb of internal capsule (right) $1785.13 \pm 155.22$ Ranterior limb of internal capsule (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (right) $2143.29 \pm 192.35$ anterior limb of internal capsule (right) $2318.29 \pm 102.39$ anterior limb of internal capsule (right) $2318.29 \pm 102.35$ anterior limb of internal capsule (right) $2318.29 \pm 102.35$ anterior limb of internal capsule (right) $2318.29 \pm 102.35$ anterior limb of internal capsule (right) $2318.29 \pm 102.35$ anterior limb of internal capsule (right) $2318.92 \pm 207.39$ anterior limb of internal capsule (right) $2318.29 \pm 192.25$ anterior limb of internal capsule (right) $2318.29 \pm 192.25$ anterior limb of internal capsule (right) $2318.29 \pm 192.25$ anterior limb of internal capsule (right) $2318.29 \pm 192.25$ anterior	PLIC L	posterior limb of internal capsule (left)	$2927.29 \pm 249.74$	$2142.37 \pm 401.62$	26.81%	<0.0001
L external capsule (left) $2986.21 \pm 235.91$ external capsule (left) $12.397.46 \pm 1277.73$ medial lemniscus (right) $962.42 \pm 119.31$ external capsule (right) $12.397.46 \pm 1277.73$ medial lemniscus (right) $962.42 \pm 119.31$ external capsule (right) $1976.04 \pm 198.51$ formix/stria terminalis (left) $1976.04 \pm 198.72$ formix/stria terminalis (left) $1785.13 \pm 155.22$ R basal forebrain (left) $1785.13 \pm 155.22$ for cerbrain R basal forebrain (left) $1785.13 \pm 155.22$ anterior limb of internal capsule (right) $1785.13 \pm 155.22$ anterior limb of internal capsule (right) $1785.13 \pm 155.22$ midbrain (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (left) $2143.29 \pm 207.18$ anterior limb of internal capsule (left) $2348.92 \pm 207.39$ ain R midbrain (right) $5102.92 \pm 207.39$ midbrain (right) $5102.92 \pm 207.39$ article midbrain (right) $5102.92 \pm 207.39$ and R posterior corona radiata (right) $5102.92 \pm 207.39$	ACR R	anterior corona radiata (right)	$13,192.63 \pm 1425.59$	$9768.41 \pm 1473.60$	25.96%	<0.0001
Lanterior corona radiata (left) $12,397.46 \pm 1277.73$ anterior corona radiata (left) $12,397.46 \pm 1277.73$ medial lemniscus (right) $962.42 \pm 119.31$ external capsule (right) $962.42 \pm 119.31$ external capsule (right) $1876.92 \pm 188.51$ terebral peduncle (teft) $1976.04 \pm 198.72$ terebral peduncle (right) $1976.04 \pm 198.72$ terebral peduncle (right) $1976.04 \pm 198.72$ Forebrain Lbasal forebrain (left)anterior limb of internal capsule (right) $2189.42 \pm 248.78$ Forebrain Rbasal forebrain (left)anterior limb of internal capsule (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (right) $2348.92 \pm 207.18$ anterior limb of internal capsule (right) $2348.92 \pm 207.39$ and Rmidbrain (right) $2313.29 \pm 192.35$ and Rposterior corona radiata (right) $2000.63 \pm 720.25$ and horicular vari of internal capsule (reft) $2313.29 \pm 192.35$	ECL	external capsule (left)	$2986.21 \pm 235.91$	$2217.41 \pm 294.36$	25.75%	<0.0001
medial lemniscus (right) $962.42 \pm 119.31$ external capsule (right) $962.42 \pm 119.31$ external capsule (right) $2969.96 \pm 217.33$ external capsule (right) $1976.04 \pm 198.72$ terebral peduncle (right) $1976.04 \pm 198.72$ Forebrain L $1976.04 \pm 198.72$ Forebrain L $1976.04 \pm 198.72$ R $1755.13 \pm 155.22$ R $1785.13 \pm 155.22$ R $1785.13 \pm 155.22$ R $177.96 \pm 155.84$ Forebrain R $2189.42 \pm 248.78$ Sorebrain R $2189.42 \pm 248.78$ T $177.96 \pm 155.84$ I $177.96 \pm 155.84$ I $177.96 \pm 155.84$ I $177.96 \pm 155.84$ I $1870.92 \pm 207.18$ anterior limb of internal capsule (right) $2143.29 \pm 207.18$ and the rest limb of internal capsule (right) $2348.92 \pm 207.139$ and Rmidbrain (right) $2348.92 \pm 207.39$ and Rposterior corona radiata (right) $200.63 \pm 720.25$ Tretrolentionlar near of internal capsule (right) $200.63 \pm 720.25$	ACR L	anterior corona radiata (left)	$12,397.46 \pm 1277.73$	$9240.81 \pm 1437.56$	25.46%	<0.0001
cexternal capsule (right)2969-96 $\pm 217.33$ Lexternal capsule (reft)1976.92 $\pm 188.51$ Lfornix/stria terminalis (left)1976.94 $\pm 198.72$ Forebrain Lbasal forebrain (left)1464.08 $\pm 131.08$ Forebrain Lbasal forebrain (left)1785.13 $\pm 155.22$ Ranterior limb of internal capsule (right)2189.42 $\pm 248.78$ Forebrain Rbasal forebrain (left)2189.42 $\pm 248.78$ Tanterior limb of internal capsule (right)2143.29 $\pm 207.18$ anterior limb of internal capsule (right)2348.92 $\pm 207.18$ and Rmidbrain (right)2348.92 $\pm 207.39$ ain Rmidbrain (right)2313.29 $\pm 192.35$ Rmidbrain (right)200.63 $\pm 720.25$ Tposterior corona radiata (right)200.63 $\pm 720.25$	MLR	medial lemniscus (right)	$962.42 \pm 119.31$	$720.85 \pm 112.27$	25.10%	<0.0001
Lccrebral peduncle (left) $1876.92 \pm 188.51$ Lccrebral peduncle (right) $1976.04 \pm 198.72$ Forebrain Lbasal forebrain (left) $1785.13 \pm 155.22$ Ranterior limb of internal capsule (right) $1785.13 \pm 155.22$ Ranterior limb of internal capsule (right) $2189.42 \pm 248.78$ Forebrain Rbasal forebrain (left) $2189.42 \pm 248.78$ Forebrain Ranterior limb of internal capsule (right) $2189.42 \pm 248.78$ Forebrain Ranterior limb of internal capsule (right) $2189.42 \pm 248.78$ Tmidbrain (right) $2189.42 \pm 248.78$ Tanterior limb of internal capsule (right) $2189.42 \pm 248.78$ Tmidbrain (right) $2189.42 \pm 248.78$ Tmidbrain (right) $2143.29 \pm 207.18$ anterior limb of internal capsule (left) $2348.92 \pm 207.39$ ain Rmidbrain (right) $2313.29 \pm 192.35$ Rposterior corona radiata (right) $5102.92 \pm 720.25$ Tretrollar nard of internal capsule (left) $2900.63 \pm 720.25$	ECR	external capsule (right)	$2969.96 \pm 217.33$	$2232.00 \pm 327.81$	24.85%	<0.0001
L $1976.04 \pm 198.72$ fornix/stria terminalis (left) $1976.04 \pm 198.72$ 1976.04 $\pm 198.72$ Forebrain Lbasal forebrain (left) $1464.08 \pm 131.08$ 185.13 $\pm 155.22$ Ranterior limb of internal capsule (right) $1464.08 \pm 131.08$ 1577.96 $\pm 155.84$ 2189.42 $\pm 248.78$ Forebrain Rbasal forebrain (left) $2189.42 \pm 248.78$ 1577.96 $\pm 155.84$ 2143.29 $\pm 207.18$ Lanterior limb of internal capsule (right) $2189.42 \pm 248.78$ 2189.42 $\pm 248.78$ 2348.92 $\pm 207.18$ anterior limb of internal capsule (left)anterior limb of internal capsule (right) $2348.92 \pm 207.18$ 2313.29 $\pm 192.35$ 300 sterior corona radiata (right)Rposterior corona radiata (right) $200.63 \pm 720.25$ $\pm 770.25$	CPL	cerebral peduncle (left)	$1876.92 \pm 188.51$	$1434.19 \pm 279.67$	23.59%	<0.0001
fornix/stria terminalis (left) $1464.08 \pm 131.08$ basal forebrain (left) $1785.13 \pm 155.22$ basal forebrain (left) $1785.13 \pm 155.22$ anterior limb of internal capsule (right) $2189.42 \pm 248.78$ basal forebrain (right) $2189.42 \pm 248.78$ basal forebrain (right) $2189.42 \pm 248.78$ basal forebrain (right) $2189.42 \pm 207.18$ midbrain (left) $2143.29 \pm 207.18$ midbrain (left) $2348.92 \pm 207.39$ midbrain (right) $2313.29 \pm 192.35$ posterior corona radiata (right) $5102.92 \pm 720.25$ retrolementicular vart of internal carsule (left) $2900.63 \pm 720.25$	CP R	cerebral peduncle (right)	$1976.04\pm198.72$	$1513.52 \pm 250.70$	23.41%	<0.0001
basal forebrain (left) $1785.13 \pm 155.22$ anterior limb of internal capsule (right) $2189.42 \pm 248.78$ basal forebrain (right) $2189.42 \pm 248.78$ basal forebrain (right) $2189.42 \pm 248.78$ basal forebrain (right) $2189.42 \pm 248.78$ anterior limb of internal capsule (left) $2189.42 \pm 207.39$ midbrain (left) $2348.92 \pm 207.39$ midbrain (right) $2313.29 \pm 192.35$ posterior corona radiata (right) $5102.92 \pm 207.39$ routien (right) $5102.92 \pm 720.25$ routien routien (reght) $2900.63 + 324.53$	Fx/ST L	fornix/stria terminalis (left)	$1464.08 \pm 131.08$	$1133.22 \pm 136.64$	22.60%	<0.0001
anterior limb of internal capsule (right) $2189.42 \pm 248.78$ rain Rbasal forebrain (right) $1577.96 \pm 155.84$ anterior limb of internal capsule (left) $2143.29 \pm 207.18$ midbrain (left) $2348.92 \pm 207.39$ midbrain (left) $2313.29 \pm 192.35$ posterior crona radiata (right) $5102.92 \pm 720.25$ posterior crona radiata (right) $2000.63 \pm 720.25$	BasalForebrain L	basal forebrain (left)	$1785.13 \pm 155.22$	$1393.04 \pm 151.01$	21.96%	<0.0001
rain R         basal forebrain (right)         1577.96 ± 155.84           anterior limb of internal capsule (left)         2143.29 ± 207.18           midbrain (left)         2348.92 ± 207.39           midbrain (right)         2313.29 ± 192.35           posterior corona ardiata (right)         5102.92 ± 720.25           methonicular mark of internal cansule (left)         2006.63 ± 720.25	ALIC R	anterior limb of internal capsule (right)	$2189.42 \pm 248.78$	$1716.78 \pm 277.87$	21.59%	<0.0001
anterior limb of internal capsule (left) $2143.29 \pm 207.18$ midbrain (left) $2348.92 \pm 207.39$ midbrain (right) $2313.29 \pm 192.35$ posterior corona radiata (right) $5102.92 \pm 720.25$ retrolenticular nart of internal cansule (left) $2000.63 \pm 720.25$	BasalForebrain R	basal forebrain (right)	$1577.96 \pm 155.84$	$1245.15 \pm 138.66$	21.09%	<0.0001
midbrain (left) $2348.92 \pm 207.39$ midbrain (right) $2313.29 \pm 192.35$ posterior corona radiata (right) $5102.92 \pm 720.25$ retrolenticular nart of internal consule (left) $2000.63 \pm 720.63$	ALIC L	anterior limb of internal capsule (left)	$2143.29 \pm 207.18$	$1697.07\pm307.27$	20.82%	<0.0001
midbrain (right) $2313.29 \pm 192.35$ posterior corona radiata (right) $5102.92 \pm 720.25$ retrolenticular part of internal consule (left) $2000.63 \pm 720.63$	Midbrain L	midbrain (left)	$2348.92 \pm 207.39$	$1877.48 \pm 322.73$	20.07%	<0.0001
posterior corona radiata (nght) $5102.92 \pm 720.25$ retralenticular net of internal cascula (left) $2000.63 \pm 7204.63$	Midbrain R	midbrain (right)	$2313.29 \pm 192.35$	$1888.7 \pm 281.50$	18.35%	<0.0001
retrolenticular part of internal cancula (left) $2900.63 \pm 204.63$	PCR R	posterior corona radiata (right)	$5102.92 \pm 720.25$	$4175.22 \pm 583.08$	18.18%	<0.0001
$\mathbf{r}_{\mathbf{r}}$	RLIC L	retrolenticular part of internal capsule (left)	$2900.63 \pm 294.63$	$2385.11 \pm 317.16$	17.77%	<0.0001

Structure		НС	WD	Volume decrease rate	P values
Abbreviation	full name				
Thalamus R	thalamus (right)	$6128.18 \pm 753.20$	$5080.11 \pm 759.68$	17.20%	<0.000]
MCP R	middle cerebellar peduncle (right)	$3053.50\pm 366.10$	$2545.74 \pm 337.98$	16.63%	0.0002
Thalamus L	thalamus (left)	$5877.66 \pm 424.71$	$4880.59 \pm 784.86$	16.58%	<0.0001
SCP R	superior cerebellar peduncle (right)	$864.25 \pm 87.07$	$722.19 \pm 92.77$	16.44%	<0.0001
RLIC R	retrolenticular part of internal capsule (right)	$2955.33 \pm 290.84$	$2494.93 \pm 324.88$	15.58%	<0.0001
SLF L	superior longitudinal fasciculus (left)	$7134.71 \pm 684.30$	$6052.41 \pm 840.49$	15.17%	<0.0001
MCP L	middle cerebellar peduncle (left)	$2797.79 \pm 303.53$	$2381.81 \pm 309.24$	14.87%	0.0001
IFO R	inferior fronto-occipital fasciculus (right)	$2035.71 \pm 151.09$	$1741.04\pm 206.92$	14.48%	<0.0001
CIR	claustrum (right)	$469.38 \pm 37.13$	$404.89 \pm 48.78$	13.74%	<0.0001
IFOL	inferior fronto-occipital fasciculus (left)	$1895.38\pm152.22$	$1640.26 \pm 238.25$	13.46%	<0.0001
SFG PFC R	superior frontal gyrus/ prefrontal cortex (right)	$9863.88 \pm 807.00$	$8559.52 \pm 1108.31$	13.22%	<0.0001
SS L	sagittal stratum (left)	$3600.79 \pm 425.58$	$3133.26 \pm 369.69$	12.98%	0.0005
SFG PFC L	superior frontal gyrus/ prefrontal cortex (left)	$10,681.38\pm932.80$	$9329.07 \pm 1253.48$	12.66%	0.0002
SFWM PFC R	subcortical white matter of the superior frontal	$7427.38 \pm 574.21$	$6564.15\pm868.70$	11.62%	0.0002
	gyrus/ prefrontal cortex(right)				
CGC L	cingulum (cingulate gyrus part) (left)	$2748.25 \pm 308.43$	$2428.85 \pm 346.11$	11.62%	<0.0001
Cerebellum WM L	cerebellum white matter (left)	$8381.50 \pm 5870$	$7422.67 \pm 688.66$	11.44%	0.0001
Cerebellum WM R WD > HC	cerebellum white matter (right)	$8987.25 \pm 720.23$	$8057.74 \pm 705.52$	10.34%	0.0003
SylTempSul L	Sylvian fissure and posterior insular sulcus (left)	$2121.67 \pm 433.84$	$2995.89 \pm 816.57$	-41.20%	<0.0001
SylTempSul R	Sylvian fissure and posterior insular sulcus (right)	$1828.75 \pm 437.36$	$2583.85 \pm 753.69$	-41.29%	<0.0001
SylFrontSul L	Sylvian fissure and anterior insular sulcus (left)	$1893.21\pm451.61$	$2677.74 \pm 904.79$	-41.44%	0.0002
III ventricle	third ventricle	$1804.25\pm440.55$	$3117.70 \pm 745.88$	-72.80%	<0.0001
Chroid LVetc R	choroid plexus of the lateral ventricle etc. (right)	$130.38\pm44.77$	$243.48 \pm 64.74$	-86.75%	<0.0001
Chroid LVetc L	choroid plexus of the lateral ventricle etc. (left)	$160.38 \pm 55.56$	$301.74 \pm 80.34$	-88.14%	<0.0001
LV Frontal R	frontal horn of the lateral ventricle (right)	$3073.38 \pm 1927.92$	$7245.26 \pm 2993.32$	-135.74%	<0.0001
LV Frontal L	frontal horn of the lateral ventricle (left)	$3251.38 \pm 2434.69$	$7729.48 \pm 3118.25$	-137.73%	<0.0001

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