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Correlation between Grades of White Matter Hyperintensities with Gray Matter Volume and Cognition in Patients with Arteriosclerotic Cerebral Small Vessel Disease

Tamer A. Kamal^a, Al Siagy A. Abd Al Azziz^b, Marwa M. Taha^b, Sherif A. Abd Al Satar^a

^a Radiodiagnosis Department, Faculty of Medicine Benha University, Egypt.

^b Radiodiagnosis Department, Faculty of Medicine Tanta University, Egypt.

Corresponding to: Marwa M. Taha. Radiodiagnosis Department, Faculty of Medicine Tanta University, Egypt.

Email: Omarhla2013@gmail.com

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Abstract:

Background: Arteriosclerotic cerebral small vessel disease (ACSVD) includes a range of syndromes affecting the brain's smallest blood vessels comprising arterioles, micro arteries, capillaries, and venules triggered by various etiologies. This study investigated cortical atrophy patterns in ACSVD by analyzing GMV variations across different WMH grades (using the Fazekas scale) through volumetric segmentation in multiple brain regions. The study also explored correlations between GMV reductions and cognitive impairment in ACSVD patients. Methods: This prospective study included 100 patients with WMH as indicative of ACSVD and 50 healthy control subjects matching age and sex distributions with the patient group. Results: Significant GMV reductions were observed in the right superior frontal and parietal lobes of ACSVD patients compared to controls (P = 0.001 and P < 0.0001, respectively), correlating with higher Fazekas scores and cognitive impairment. Conclusion: WMH-related GMV reductions, especially in frontal and parietal regions, contribute to cognitive impairment in ACSVD, highlighting the potential of advanced imaging for early detection and intervention.

Keywords: White Matter Hyperintensities; Gray Matter Volume; Cognition; ACSVD.

Introduction

ACSVD affects small cerebral blood vessels, including arterioles, micro arteries, capillaries, and venules, contributing to neurological morbidity worldwide. ACSVD is linked to about 45% of dementia cases and 20% of strokes globally, highlighting its significant neurological impact^[1].

Key MRI findings in ACSVD include WMHs, lacunar infarcts, and brain atrophy, which serve as imaging biomarkers of disease progression ^[2]. These features, especially WMHs, are prevalent in the elderly ^[3]. Whereas some ACSVD patients experience cognitive changes, from mild impairment to dementia, others show no signs of cognitive deterioration ^[4-6]. Recent evidence suggests that cognitive impairment in ACSVD is mediated through complex corticalsubcortical networks disruption^[7]. In a previous study image analysis technique was utilized to further characterize the cortical atrophy pattern in ACSVD and identify the between correlation gray matter changes and WMH^[8].

Earlier research has demonstrated that elevated WMH grades, as assessed by the Fazekas scale, correlate with reduced GMV throughout the brain. This reduction is particularly noticeable in the frontal and temporal lobes, para hippocampal gyrus, and hippocampus, and occurs independently of age ^[9]. Additional studies have established a strong link between elevated WMH volume and diminished GMV in the thalamus ^[10]. Moreover, investigations have highlighted the connection between GMV in frontal and temporal areas, comprising the hippocampus and thalamus, and cognitive function^[11].

However, the specific correlations between WMH severity, GMV reduction, and cognitive impairment in ACSVD remain underexplored. This study aims to bridge this gap using advanced volumetric segmentation techniques to enable precise quantification of brain volumes. enhancing the detection of subtle cortical atrophy in a variety of neurological conditions. This method should complement visual evaluation of brain structural images, with the goal of enhancing the detection of both focal and subtle brain pathologies ^[12]. Cortical reconstruction and gray matter volumetric segmentation utilizing the Free Surfer has been shown to be costeffective and highly beneficial. especially in large-scale cross-sectional and longitudinal neurological studies [13] Moreover, its automatic segmentation has been demonstrated to be as accurate manual as measurements performed by experts [14]

This study's purpose was to characterize the pattern of cortical atrophy in ACSVD by identifying brain regions with significant differences in GMV in patients with different grades of WMH (according to Fazekas scale) through volumetric segmentation of gray matter by image analysis techniques in different brain regions. Furthermore, understanding whether correlations existed between GMV in different brain regions and cognitive impairment.

Methods

This prospective study included 100 ACSVD patients (61 males, 39 females) with WMH and 50 age- and sex-matched healthy controls, conducted between September 2022 and July 2024 at the Diagnostic Radiology Department at Banha University.

Institutional ethical approval and Informed consent were obtained from all participants following a comprehensive explanation of study objectives, procedures, potential risks, and benefits, ensuring that subjects were thoroughly informed before consenting to participate.

Inclusion criteria: (1) Age \geq 55 years, (2) Presence of WMHs suggestive of ACSVD, (3) No history of traumatic brain injury or neurodegenerative diseases. (4) Control group inclusion criteria included normal cerebral MRI findings, normal performance on neuropsychological assessments.

Exclusion criteria were as follows: 1) Non-ischemic cerebral MRI abnormalities, 2) Major neurological or psychiatric conditions, 3) Dementia diagnosis as patients scoring below 20 on the Mini-Mental State Examination (MMSE) for primary school education or less than 24 for those with junior school education or higher, 4) significant head trauma, 5) MRI contraindications, 7) Control group participants were excluded if they had psychological or physical severe diseases or if they lacked formal liberal education.

All studied cases were subjected to the following: Clinical evaluation, Neuropsychological Assessments, Diagnostic Imaging, Fazekas Grading, and Neuroimaging Protocol (MRI Scanning).

Clinical Evaluations: including comprehensive medical history and a series of neuropsychological tests designed to assess various cognitive domains.

Neuropsychological Assessments: All patients underwent extensive neuropsychological assessments within one week of their MRI examinations. The assessments include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), both of which are validated tools for evaluating cognitive function across various

domains. Scores from these assessments were recorded, and based on the results, all the participants were classified into three groups that were matched for age, sex, and education level: ACSVD patients with normal cognition (ACSVD-NC), ACSVD patients with mild cognitive impairment (ACSVD-MCI), and a normal control group. MCI was defined as performance falling by more than 1.5 standard deviations below the population norm in any cognitive domain, excluding those who met the criteria for dementia.

Diagnostic Imaging: The diagnosis of ACSVD in patients was relied on detecting WMH and ruling out noninfarcts T2-weighted lacunar on (T2WI) and T2FLAIR images. Lacunar infarcts were defined as focal hypo intensities (≤ 15 mm in diameter) on T1-weighted images (T1WI) and as hyperintensities on both T2WI and T2-FLAIR scans.

Fazekas Grading: The grading of WMH was done with the Fazekas scale, which assesses the white matter changes severity relying on imaging characteristics.

WMH severity was classified based on Fazekas scores, summing periventricular and deep WMH grades into mild (1-2) and moderate-severe (3–6). Previous research indicates that a Fazekas score of 3 is a critical threshold where significant injury to white matter microstructures begin to manifest. Therefore, participants with WMH were categorized into 2 groups relying on their total Fazekas scores: (Group A) WMH scores of 1-2 points and (Group B) scores of 3-6 points. This classification facilitates a deeper understanding of how varying levels of WMH impact cognitive function. Table 1

| Tuble I. I allent group elassification according to I azeras score. | | | | |
|---|---------|-----------------|--|--|
| | Group A | Group B | | |
| Fazekas score | 1-2 | 3-6 | | |
| WMH Severity | Mild | Moderate- Sever | | |
| Number of patients | 17 | 83 | | |
| Cognitive score | 20-26 | 16-22 | | |

Table 1: Patient group classification according to Fazekas score.

Neuroimaging **Protocol: MRI** Scanning: Brain MRI was conducted using a 1.5 Tesla scanner with a standard quadrature head coil. employing sagittal 3D T1-weighted sequences for volumetric segmentation with 1.0 mm slice thickness and 0.9375 mm pixel spacing. The imaging parameters included axial inversion recovery preparation, spoiled gradient recall, 12 ms repetition time, 2.8 ms echo time, 600 ms inversion time, 256 \times 256 matrix size. These parameters were chosen to optimize image quality and resolution, facilitating accurate assessment of brain structures.

GMV **Analysis:** Cortical and subcortical structures underwent regional restoration and segmentation utilizing the FreeSurfer image analysis suite v6. This software is widely used in neuroimaging research for its ability to accurately delineate brain structures. The outputs from FreeSurfer were meticulously inspected for errors of misclassifications ensure to data integrity. Previous studies have established that higher WMH grades correlate with lower GMV throughout the brain, particularly in regions such as the frontal and temporal lobes, the para hippocampal gyrus, hippocampus, and thalamus. Consequently, this study concentrated specifically on these brain regions to investigate the correlation between WMH severity and cognitive performance.

Segmentation Process: The segmentation process involved several detailed stages, beginning with the cortical surface reconstruction. Normalized intensity images were created and corrected for variations in signal intensity caused by magnetic field inhomogeneity. Voxels beyond the cerebral cortex, such as the skull, were removed before segmentation began. The segmentation process utilized geometric structures at the interface of gray and white matter to differentiate between left and right hemispheres and to separate cortical from subcortical structures accurately. The resulting cortical volume was represented using а triangular tessellation, which was deformed to more accurately reflect the gray and white matter interface as well as the pial surface. Following reconstruction, this volume was registered to a spherical atlas and parcellated into regions in accordance with sulcal and gyral structures. Desikan's Atlas was utilized for defining regions of interest ensuring comprehensive (ROIs). coverage of the relevant brain areas.

Image Interpretation: The interpretation of MRI images was conducted by two expert radiologists with over 10 years of experience in neuroradiology. Their expertise ensured accurate identification of WMH, lacunar infarcts, and other relevant findings.

Code Number: MD 2-8-2022. Statistical analysis

Data were analyzed using SPSS version 26 (IBM©, Armonk, NY, USA), with quantitative data presented as mean \pm SD and analyzed using Student's t-tests and ANOVA. Categorical data were presented as frequencies and percentages, with Chisquare or Fisher's exact tests applied. Statistical significance was set at P <0.05. This comprehensive statistical approach ensured robust comparisons between groups and accurate assessment of both quantitative and qualitative variables, providing a solid foundation for interpreting the study's findings.

Results

Patients were significantly older than which may influence controls. cognitive outcomes. No significant difference in sex distribution. Fazekas scores were significantly higher in patients, indicating a more extensive WMH burden (P < 0.001). Significant brain atrophy was observed in ACSVD patients, with lower total brain volume compared to controls (P < 0.001). Patients demonstrated significantly reduced cognitive performance compared to controls. Table 2 The left lateral ventricle volume and the left inferior lateral ventricle were significantly larger in patients in comparison with controls. The left cerebellum white matter and the left cerebellum cortex volume in patients were significantly lower than the left controls. The caudate was

controls. Patients had significant differences in the third and fourth ventricles volume compared to controls, but no

significantly larger in patients than in

significant differences were found in volumes of brain stem. left ventral diencephalon region (VDC) and left accumbens area. Patients showed less volumes of left hippocampus and left amygdala while more CSF volume compared to controls. Patients had larger left choroid plexus and right lateral ventricle volumes, while the right inferior lateral ventricle volumes were similar. However, the right cerebellum white matter volume was significantly lower in patients. No significant differences were found in the right thalamus, caudate, putamen, hippocampus or amygdala. Table 3 found no The study significant difference in left brainstem, caudal anterior cingulate, entorhinal, fusiform, and inferior temporal volume between patients and controls. However, the left caudal middle frontal volume showed a significant reduction in patients compared to controls. The left-handed cuneus volume also showed significant reductions. In terms of visual processing, left lateral occipital, lateral orbitofrontal, and lingual volumes were significantly diminished in patients (p < 0.001). Left pericalcarine, precentral and left postcentral volumes showed significant reductions. Table 4

| studied groups. | | | |
|---------------------------------|-----------------|-----------------|-----------------|
| Variable | Patients Group | Controls Group | <i>p</i> -value |
| | (Mean ± SD) | $(Mean \pm SD)$ | |
| Age (years) | 72.1 ± 8.2 | 68.4 ± 7.4 | 0.02* |
| Sex (Male/Female) | 61/39 | 25/25 | 0.34 |
| Fazekas Score (0-6) | 2.1 ± 0.8 | 0.5 ± 0.6 | < 0.001* |
| Brain Volume (cm ³) | $1,200 \pm 150$ | $1,400 \pm 180$ | < 0.001* |
| Cognitive Score (0-30) | 21 ± 5 | 27 ± 3 | < 0.001* |

 Table 2: Demographic data, Fazekas Score, Brain Volume, and Cognitive Score of the studied groups

*: statistically significant as *p* value <0.05.

| Table 3: Deep gray matter and other brain structures volumes in patients and cor | ntrols. |
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| structures volumes Mean Std. Deviation Near Std. Deviation Value Lot II Lat Venti Let Venti 20844 786667 80(13) 975685667 417,880201 011 # Lat Right Carbonic 48630,040000 4854,582414 51955,156667 50(87,741442 0.011 # Lat Cerebellum White Matter 1218,093333 875,5304130 576,856667 50(87,741442 0.012 * Lat Rumane 4366,0164667 63(8,4571422 4122,610000 488,4850441 592,345038 0.002 * Lat Rumane 4366,016667 270,891520 1884,466667 271,991809 0.036 * And Name 1972,766667 226,12143148 2023,000000 721,491809 0.037 * Brain Stem 1984,466667 226,12143148 2023,0000000 220,482393 90,007 * Left Hypercampus 4307,02000 77,4702011 441,160000 93,852277 0,153 Left Martin Discopenhau 499,670000 73,4702011 441,160000 93,85227 0,000 * Left Martin Discopenhau (CPC) 343,5057 74, | Deep gray matter and other brai | n | Patients | | Controls | | D voluo |
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| Left Pallidum 1732 76667 276 8919263 1884 466667 1761 1000 583 2311058 0.015* aft Ventricle 1893 276667 650 0255349 1471 130000 658 2311058 0.015* afth Ventricle 2475 450000 671 4938179 1711 1716667 444 687495 -0.0001* Left Amygdala 1249 873333 395 6750188 3740.916667 862 2256905 -0.001* Left Acumbens area 409 670000 3405 5520865 1526.33333 297 600223 -0.0001* Left Acumbens area 409 670000 373 472167 3461.357 397 712 -0.001* Left vessel 59 496667 57278852 696.136667 1928.330510 228 Left vessel 59 496667 526.815945 500.07333 438.44829 0.001* Right Carebellum White Matter 11477.19333 1375.7076375 13976 (14667 1328.305616 -0.0001* Right Carebellum White Matter 1477.193333 1375.7076375 13976 (14667 1328.9305616 -0.0001* Right Carebellum White Matter 1477.193333 | Left Putamen | | 4366.046667 | 658.4571422 | 4427.650000 | 557.0427878 | 0.697 |
| 3rd Ventricle 1893.276667 659.0253549 1471.320000 658.2311058 0.015* Han Ventricle 2475.450000 671.4938179 1711.716667 444.6587495 -0.0001* Brain Stem 19844.666667 2261.243148 20239.000000 2260.0000 58.025770 0.0001* Left Hippocampus 3407.623333 196.5520865 1526.343333 295.7570186 444.6587470 0.0002* Left Accumbens area 409.670000 73.4702011 441.160000 93.8502277 0.103 Left ventral Diencephalon (VDC) 3435.057 377.77852 696.136667 199.468624 0.019* Right Lateral Ventricle 1823.733333 8925.6990942 13175.12333 767.8519232 0.016* Right Cerebellum Write Matter 11477.193333 1875.7076375 13976.046667 192.848249 0.006* Right Cerebellum Write Matter 11477.193333 1875.7076375 13976.046667 192.848249 0.001* Right Cerebellum Write Matter 11477.193333 1875.7076375 13976.046667 143.6782000 0.011* <t< td=""><td>Left Pallidum</td><td></td><td>1732.766667</td><td>276.8919263</td><td>1884.466667</td><td>271.6918695</td><td>0.036*</td></t<> | Left Pallidum | | 1732.766667 | 276.8919263 | 1884.466667 | 271.6918695 | 0.036* |
| idit Ventricle 2475.450000 671.4938179 1711.716667 444.6587495 -0.0001* Brain Stem 1984.466667 2201.2143148 2023.00000 2204.682897 0.4977 Left Amygdala 1249.873333 395.6750188 3740.916667 486.2256905 0.002* CSF 1352.660000 360.7885297 1092.176667 288.2934570 0.012* Left Acumbens area 400.670000 73.4702011 441.160000 93.8502277 0.153 Left Acumbens area 409.670000 327.778252 696.136667 199.488294 0.001* Left vessel 92.466667 552.64815945 560.073333 438.48291 0.001* Right Lerenblum White Matter 11477.193333 1875.7076375 13976.046667 192.8305616 -0.0001* Right Cerebellum White Matter 14875.7076375 13976.04667 192.8305616 -0.0001* Right Cerebellum White Matter 1477.193333 1875.7076375 13976.04667 192.8305616 -0.0001* Right Cerebellum White Matter 14875.7076375 1376.104667 1 | 3rd Ventricle | | 1893.276667 | 659.0253549 | 1471.320000 | 638,2311058 | 0.015* |
| Brain Stem 19844.666667 22612.143148 20239.000000 2204.6828997 0.497 Left Hyppocampus 3407.623333 396.5750188 374.09116667 486.2256055 0.0005* Left Armygdala 1249.873333 196.5520865 1526.343333 297.6902923 <0.0001* | 4th Ventricle | | 2475.450000 | 671.4938179 | 1711.716667 | 444.6587495 | < 0.0001* |
| $ \begin{array}{c} Left Amygdal \\ Left Accumbers area \\ Left Accumbers area \\ Left Accumbers area \\ Left Accumbers area \\ Left Nentral Diencephalon (VDC) \\ 3455.057 \\ 3455.056 \\ 3455.050 \\ 3455.056 \\ 3455.050 \\ 34555.050 \\ 34555.050 \\ 34555.050 \\ 34555.050 \\ 34555.050 \\ 34555.050 $ | Brain Stem | | 19844 666667 | 2261 2143148 | 20239 000000 | 2204 6828997 | 0 497 |
| $\begin{array}{llllllllllllllllllllllllllllllllllll$ | Left Hippocampus | | 3407 623333 | 395 6750188 | 3740 916667 | 486 2256905 | 0.005* |
| $\begin{array}{c} CSF & \begin{tabular}{ c c c c c c c c c c c c c c c c c c c$ | Left Amygdala | | 1249.873333 | 196.5520865 | 1526.343333 | 297.6902923 | < 0.0001* |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | CSF | | 1352 660000 | 360 7885297 | 1092 176667 | 268 2934570 | 0.002* |
| Left Ventral Diencephalon (VDC) 3435.037 374.1657 , 3861.357 393.7212 , $<0.0001^{\circ}$ Left vessel 59.49667 , 572.684 , 44.74000 , 42.8358261 , 0.228 Left vessel Left choroid plexus 83.32000 , 237.7218252 , 696.136667 , 199.4686294 , 0.019° Right Lateral Ventricle 18523.73333 , 8925.690942 , 13175.12333 , 767.8519232 , 0.016° Right Lateral Ventricle 18523.73333 , 8925.690942 , 13175.12333 , 767.8519232 , 0.000° Right Carebellum Cortex 48081.54667 , 5294.1989529 , 52291.94000 , 5177.8431720 , 0.000° Right Carebellum Cortex 48081.54667 , 5294.1989529 , 52291.94000 , 5177.8431720 , 0.001° Right Carebellum Cortex 48081.54667 , 5294.1989529 , 52291.94000 , 5177.8431720 , 0.001° Right Patamen 4466.410000 , 671.5917296 , 4374.53667 , 433.6782000 , 0.001° Right Patamen 4466.410000 , 671.5917296 , 4374.53667 , 433.6782000 , 0.001° Right Patamen 4466.410000 , 071.5917296 , 4374.536667 , 431.8453559 , 0.539 Right Adludm 1707.470000 , 181.51074 , 164.8403333 , 244.3887808 , 0.001° Right Adludm 156.6220000 , 181.51074 , 164.8403333 , 244.3887808 , 0.001° Right Acumbens area 418.043333 , 63.3087545 , 445.766667 , 70.5855965 , 0.115 Right Ventral Diencephalon (VDC) 3365.620000 , 442.2644009 , 3772.516667 , 138.9337719 , $<0.0001^{\circ}$ Right ventral Diencephalon (VDC) 3365.620000 , 442.2644009 , 3772.516667 , 139.93874217 , $<0.0001^{\circ}$ Right ventral Diencephalon (VDC) 350.56000 , 50.38006517 , 173.773333 , 42.0659493 , $<0.0001^{\circ}$ C Diectrior 915.386667 , 154.7409687 , 993.58667 , 139.93874217 , $<0.0001^{\circ}$ C Mid Posterior 915.386667 , 1594.7404848 , 527.516667 , 138.783389 , 0.0001° C C Mid Posterior 915.386667 , 1594.744848 , 527.516667 , 138.783389 , 0.0001° C C Mid Posterior 915.386667 , 1594.7409687 , 993.78667 , 1399.3884217 , $<0.0001^{\circ}$ C C Mid Posterior 915.386667 , 1594.7409687 , 993.72667 , 242.0264174 , 0.141 C C Central 974.936675 , 988.7557 , 773.6 | Left Accumbens area | | 409 670000 | 73 4702011 | 441 160000 | 93 8502277 | 0.153 |
| $\begin{array}{c} {\rm Left exsel} \\ {\rm Left choroid plexus} \\ {\rm Left choroid plexus} \\ {\rm Right Lateral Ventricle} \\ {\rm Left choroid plexus} \\ {\rm Right Lateral Ventricle} \\ {\rm Right Lateral Ventricle} \\ {\rm Right Cerebellum White Matter} \\ {\rm H477, 193333} \\ {\rm H27, 1933333} \\ {\rm H27, 19333333} \\ {\rm H21, 123, 123, 123, 123, 123, 123, 123, 1$ | Left Ventral Diencephalon (VDC) | | 3435.057 | 374 1657 | 3861 357 | 393 7212 | <0.0001* |
| Left choroid plexus 33.320000 $237.772822 696.136627$ 199.4686294 $0.010*$ Right Lateral Ventricle 18223.73333 8225.6990942 13175.12333 767.8519232 $0.016*$ Right Lateral Vent 1247.1793333 1875.7076375 13976.046667 192.89305616 $<0.0001*$ Right Carebellum Cortex 48081.546667 562.6815945 500073333 4767.8519232 $0.0001*$ Right Carebellum Cortex 48081.546667 592.4815945 500073333 475.7076375 13976.046677 192.89305616 $<0.0001*$ Right Carebellum Cortex 48081.546667 5294.1989529 52921.940000 644.1725029 $0.001*$ Right Carebellum Cortex 48081.546667 5294.1989529 52921.940000 644.1725029 $0.001*$ Right Palidum 1707.470000 277.8465641 1846.230000 285.1988467 0.061 Right Palidum 1707.470000 277.8465641 1846.230000 439.1433 $0.037*$ Right Angudala 1456.620000 181.5100347 1648.403333 439.1433 $0.037*$ Right Angudala 1456.620000 181.5100347 1648.403333 439.1433 $0.001*$ Right Angudala 1456.620000 181.5100347 1648.403333 191.0248810 $0.037*$ Right Angudala 1356.607 3325.520000 422.2644009 377.2516667 $378.9337719 < 0.0001*$ Right Accumbens area 418.043333 63.3087545 445.766667 70.5855965 0.115 Right Ventral Diencephalon (VDC) 3365.620000 442.2644009 377.2516667 $378.9337719 < 0.0001*$ Right choroid plexus 873.330000 303.4038030 733.965333 191.0248810 $0.038*$ 500 + 0000 50.3806517 173.773333 $42.0659493 < 0.00001*CC Mid Posterior 915.386667 59.876557 473.610000 134.8873749 0.0001*CC Mid Posterior 915.386667 59.876557 473.610000 134.873739 0.0001*CC Mid Posterior 915.386667 59.876557 473.610000 134.873749 0.0001*CC Mid Posterior 915.386667 59.876557 473.610000 134.873749 0.006*CC Mid Posterior 915.386667 59.876557 473.610000 134.873749 0.0001*CC Mid Posterior 915.386667 59.876557 473.610000 134.873739 0.0001*CC Mid Posterior 915.386667 59.876557 473.610000 134.8873749 0.0001*CC Mid Anteri$ | Left vessel | | 59 496667 | 50 5798684 | 44 740000 | 42 8358261 | 0.228 |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | Left choroid plexus | | 833 320000 | 237 7278252 | 696 136667 | 199 /68629/ | 0.019* |
| Right Inf Lat Vent 1022.0505 b 1022.057022 1017.012333 b 1022.057022 1017.012333 b 1022.05702 Right Cerebellum White Matter 11477.193333 1875.7076375 13976.046667 1928.9305616 <0.0001* | Right Lateral Ventricle | | 18523 733333 | 8025 6000042 | 13175 123333 | 7667 8510737 | 0.019 |
| | Right Inf L at Vent | | 021 166667 | 562 6815045 | 560 073333 | 123 8048240 | 0.016* |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | Right Coroballum White Matter | | 11477 102222 | 1975 7076275 | 12076 046667 | 1020 0205616 | <0.000 |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $ | Pight Coroballum Cortay | | 11477.195555 | 5204 1080520 | 52021 040000 | 5107 8/31720 | <0.0001* |
| Ngint Findations Froper 010, 75000 721, 730433 010, 73000 721, 730433 000, 74, 723020 0.001* Right Caudate 3880, 31333 986, 8303340 3203, 156667 433, 6782000 0.001* Right Putamen 4466, 410000 671, 5917296 4374, 536667 433, 6782000 0.001* Right Pallidum 1707, 470000 277, 8465641 1846, 23000 285, 198467 0.061 Right Accumbens area 1456, 620000 181, 5100347 1648, 403333 244, 388708 0.001* Right Ventral Diencephalon (VDC) 3365, 520000 442, 2644009 3772, 516667 70, 5855965 0.115 Right ventral Diencephalon (VDC) 3365, 520000 0.00 0.000 1004, 065846 1928, 636667 1399, 3894217 0.0001* Optic Chiasm 250, 960000 50, 380667 154, 7409687 933, 586667 242, 0264174 0.141 CC Mid Posterior 415, 713333 108, 1424818 527, 516667 138, 7833839 0.001* CC Mid Anterior 374, 936667 547, 47096877 93, 586667 242, 026 | Right Thelemus Droper | | 6102 750000 | 721 1000/22 | 52921.940000 6705 150000 | 664 1725020 | 0.001* |
| Ngint Catudate 3600.51333 901.50340 3200.51300 320.62000 0.001^{-1} Right Pallidum1707.470000 277.8465641 1846.230000 285.1988467 0.061 Right Pallidum1707.470000 277.8465641 1846.230000 285.1988467 0.061^{-1} Right Hippocampus 355.697 382.4357 3783.200 439.1433 0.001^* Right Amygdala 1456.620000 181.5100347 1648.40333 244.3887808 0.001^* Right Accumbens area 418.64333 63.3087545 444.366667 70.5855965 0.115 Right vessel 37.013333 29.1351989 26.240000 19.0820117 0.096 Right vessel 873.33000 33.403803 733.963333 191.0248810 0.038^* Sth Ventricle 0.00 0.00 0.000 0.103 0.386 0.176 WM hypointensities 11660.706667 11640.6685846 1928.636667 139.3894217 -0.0001^* CC Mid Posterior 915.386667 154.7409687 93.386667 24.0264174 0.141 CC Central 397.420000 71.6994753 477.700000 134.5873749 0.006^* CC Anterior 338.180000 162.777295 903.726667 219.2479370 0.194^* Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 0.045^* Ce Anterior 838.180000 162.777295 903.726667 219.2479370 0.194^* Brain Seg Vol V | Right Caudata | | 2000 212222 | 121.1900433 | 2202 156667 | 122 6782000 | 0.001* |
| Ngin Pulanien 440.410000 017.971290 447.35007 401.3423539 0339 Right Pallidum1707.470000 277.8465641 1846.230000 285.1988467 0.061 Right Acumbens area 1456.620000 181.5100347 1648.40333 244.3887808 $0.001*$ Right Acumbens area 418.04333 63.3087545 445.766667 70.5855965 0.115 Right ventral Diencephalon (VDC) 3365.620000 442.2644009 $377.25.16667$ 70.5855965 $0.1001*$ Right vessel 37.013333 29.1351989 26.240000 19.0220117 $0.0001*$ Right vessel 37.013333 $20.339.63333$ 191.0248810 $0.033*$ Sth Ventricle 0.000 0.000 0.000 0.3866 $1157.57.57.56667$ 1399.3894217 $<0.0001*$ Optic Chiasm 250.960000 50.3806517 177.773333 42.0659493 $<0.0001*$ CC Posterior 915.386667 154.7409687 993.586667 124.20264174 0.141 CC Canterior 374.936667 59.8676557 473.610000 123.3682806 $<0.0001*$ CC Anterior 374.936667 59.8676557 473.610000 123.3682806 $<0.0001*$ CC Anterior 838.180000 162.777295 93.726667 219.2479370 0.194 Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 $0.045*$ Brain Seg VolNot 1008120.60 97739.058 1063076.47 199351.359 | Right Dutemon | | 3000.313333 | 900.0303340 671 5017206 | 3203.130007 | 455.0762000 | 0.001 |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $ | Right Pollidum | | 4400.410000 | 071.3917290 | 43/4.330007 | 401.0433339 | 0.339 |
| Agin Inprocampus $352,00.97$ $362,437$ $435,200$ $439,1433$ $43,387808$ 0.001^* Right Accumbens area418,043333 $63,3087545$ $445,766667$ $70,5855965$ 0.115 Right Accumbens area418,043333 $63,3087545$ $445,766667$ $70,5855965$ 0.115 Right Ventral Diencephalon (VDC) $3365,620000$ $442,26440009$ $3772,516667$ $78,9337719$ $<0.0001^*$ Right vessel $37,013333$ $29,1351989$ $26,240000$ $19,0820117$ 0.096 Right choroid plexus $873,330000$ $303,4038030$ $733,963333$ $191,0248810$ 0.038^* Optic Chiasm $250,960000$ $50,3806517$ $173,7733333$ $42,0659493$ $<0.0001^*$ Optic Chiasm $250,960000$ $50,3806517$ $173,773333$ $42,0659493$ $<0.0001^*$ CC Central $397,420000$ $14,624818$ $527,516667$ $138,7833839$ 0.001^* CC Central $397,420000$ $14,624818$ $527,516667$ $138,7833839$ 0.001^* CC Anterior $838,180000$ $162,7772955$ $903,726667$ $219,2479370$ 0.194 Brain Seg Vol $1057036,83$ $106927,6557$ $473,610000$ $123,3682806$ $<0.0001^*$ Cr Anterior $838,180000$ $162,7772955$ $903,72667$ $219,2479370$ 0.194 Brain Seg Vol $1057036,83$ $106927,657$ $473,610000$ $123,3682806$ $<0.0001^*$ Cr AnteriorNot $1008120,60$ 97739.058 $1063076,47$ $109351,359$ 0.0 | Right Hinnessemnus | | 2556 607 | 277.0403041 | 2782 200 | 203.1900407 | 0.001 |
| Argin Anryguna14.0.020000161.31003471646.403533244.38078080.001Right Accumbens area418.04333363.3087545445.766667778.9337719<0.0001* | Right Amugdala | | 1456 620000 | 302.4337 191 5100247 | 3703.200 1649 402222 | 439.1433 | 0.057* |
| | Right A coumbons area | | 1430.020000 | 101.3100347 | 1040.405555 | 244.300/000 | 0.001 |
| Right vestel3503.02000 442.2644009 $577.2.16067$ $578.3537/15$ $<0.0001^{\circ}$ Right vestel37.01333329.1351198926.24000019.0820117 0.0966 Right vestel0.000.0000.100.3860.176WM hypointensities11660.70666711604.06858461928.6366671399.3894217 $<0.0001^{*}$ Optic Chiasm250.96000050.3806517173.77333342.0659493 $<0.0001^{*}$ CC Posterior915.386667154.7409687993.586667242.0264174 0.141 CC Mid Posterior415.713333108.1424818527.516667123.368206 $<0.0001^{*}$ CC Cantral397.42000071.6994753477.070000123.368206 $<0.0001^{*}$ CC Anterior838.180000162.7772995903.726667219.2479370 0.194 Brain Seg Vol1057036.83106927.6551095200.10109800.967 0.065^{*} Certar Vol1008120.6097739.0581063076.47109351.359 0.045^{*} Parain Seg Vol109318.6719926.848224365.5720886.643 $<0.0001^{*}$ Cortex Vol193918.6719926.848224365.5720886.643 $<0.0001^{*}$ Lh Cerebral White224324.4725912.423213984.0330639.288 0.163 Cerebral White224324.4725912.423213984.0330639.288 0.163 Cerebral White224324.4725912.423213984.03 30639.288 0.163 Cerebral White224324.47< | Right Ventral Dispensional (VDC | ``` | 418.045555 | 05.508/345 | 443./0000/ | 70.3833903 | 0.113 |
| Right choroid plexus $3.7.013535$ 29.1351989 26.240000 19.0220117 0.096 Sth Ventricle 0.00 0.000 0.000 0.10 0.386 0.176 WM hypointensities 11660.706667 11604.0685846 1928.636667 1399.3894217 $<0.0001*$ Optic Chiasm 250.960000 50.3806517 173.773333 42.0659493 $<0.0001*$ CC Posterior 915.386667 154.7409687 993.586667 242.0264174 0.141 CC Chid Posterior 415.713333 108.1424818 527.516667 138.7833839 $0.001*$ CC Canterior 374.936667 59.8676557 473.610000 123.3682806 $<0.0001*$ CC Anterior 838.180000 162.7772995 903.726667 219.2479370 0.194 Brain Seg Vol 1057036.83 106927.656 1096200.10 109800.967 0.167 Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 $0.045*$ Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 $0.045*$ Cretex Vol 193918.67 19926.848 224365.57 2056.643 $<0.0001*$ Lh Cerebral White 224764.17 28654.251 215306.07 29886.351 0.216 Rh Cerebral White 224324.47 25912.423 213984.03 30639.288 0.163 Suparatentorial Vol 50380.7 5618.180 53040.20 5413.846 0.176 Suparatentorial Vol | Right ventral Diencephaton (VDC |) | 3303.020000 | 442.2044009 | 3//2.31000/ | 5/6.955//19 | < 0.0001* |
| Right chorold pixels 875.35000 305.403605 735.963535 191.0248810 0.038^{*} Sth Ventricle0.000.0000.100.3860.176WM hypointensities 11660.706667 11604.0685846 1928.636667 1399.3894217 $<0.0001*$ Optic Chiasm 250.960000 50.3806517 173.773333 42.0659493 $<0.0001*$ CC Posterior 915.386667 154.7409687 993.586667 242.0264174 0.141 CC Mid Posterior 415.713333 108.1424818 527.516667 138.7833839 $0.001*$ CC Central 397.420000 71.6994753 477.070000 123.582806 $<0.0001*$ CC Anterior 374.93667 59.867557 473.610000 123.3682806 $<0.0001*$ CC Anterior 838.180000 162.7772995 903.726667 219.2479370 0.194 Brain Seg VolNot 1008581.90 97810.849 1063550.63 109926.233 $0.045*$ Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 $0.045*$ Vent SurfNot 1008120.60 97739.058 1063076.47 109351.359 $0.001*$ (Left) Lh Cortex Vol 194936.83 2119.2432 21394.03 30639.288 0.163 Cortex Vol 193918.67 19926.848 224365.57 20586.643 $<0.0001*$ Lh Cerebral White 224764.17 28654.251 215306.07 29886.351 0.216 Rh Cerebral White 224 | Right vessel | | 37.013333 | 29.1351989 | 20.240000 | 19.0820117 | 0.090 |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $ | Fight choroid plexus | | 8/3.330000 | 303.4038030 | / 33.903333 | 191.0248810 | 0.038* |
| WM hypolitensities 11600,/06607 11604,065346 1928,050607 1399,3594217 <0.0001* | Stri Ventricie | | 0.00 | 0.000 | 0.10 | 0.380 | 0.1/0 |
| Optic Cniasm 250.90000 50.3806517 175.775353 42.0059493 <0.0001* | w M hypointensities | | 11000./0000/ | 11004.0085840 | 1928.03000/ | 1399.3894217 | <0.0001* |
| CC Posterior915.380607 134.749087 995.380607 242.0264174 0.141 CC Mid Posterior 415.713333 108.1424818 527.516667 138.7833839 0.001^* CC Central 397.420000 71.6994753 477.070000 134.5873749 0.006^* CC Mid Anterior 374.936667 59.8676557 473.610000 123.3682806 $<0.0001^*$ CC Anterior 838.180000 162.7772995 903.726667 219.2479370 0.194 Brain Seg Vol 1057036.83 106927.656 1096200.10 109800.967 0.167 Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 0.045^* Vent SurfNot 1008120.60 97739.058 1063076.47 109351.359 0.045^* (Left)Lh Cortex Vol 194036.83 21119.643 222046.67 21432.283 $<0.0001^*$ (Left)Lh Cortex Vol 193918.67 19926.848 224365.57 20586.643 $<0.0001^*$ Lh Cerebral White 224764.17 28654.251 215306.07 29886.351 0.216 Matter Vol 449088.50 54198.588 429290.17 60405.048 0.187 Sub Cort Gray Vol 51088.07 5618.180 53040.20 5413.846 0.176 Sub Cort Gray Vol 51088.07 5618.180 53040.20 5413.846 0.176 Supratentorial Vol Not Vent 890593.90 91466.531 931750.57 1000703.482 0.289 Supratentorial Vol | Optic Chiasm | | 250.960000 | 50.3806517 | 1/3.//3333 | 42.0659493 | <0.0001* |
| CC C mitral 415.71333 108.142818 527.516667 138.783839 0.001^{*} CC Central 397.420000 71.6994753 477.070000 134.5873749 0.006^{*} CC Mid Anterior 374.936667 59.8676557 473.610000 123.3682806 $<0.0001^{*}$ CC Anterior 838.180000 162.7772995 903.726667 219.2479370 0.194 Brain Seg Vol 1057036.83 106927.656 1096200.10 109800.967 0.167 Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 0.045^{*} Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 0.045^{*} (Left)Lh Cortex Vol 194036.83 21119.643 222046.67 21432.283 $<0.0001^{*}$ (Right) Rh Cortex Vol 193918.67 19926.848 224365.57 20586.643 $<0.0001^{*}$ Cortex Vol 387955.50 40807.923 446412.13 41589.586 $<0.0001^{*}$ Matter Vol 224764.17 28654.251 215306.07 29886.351 0.216 Matter Vol 449088.50 54198.588 4229290.17 60405.048 0.187 Sub Cort Gray Vol 51088.07 5618.180 53040.20 5413.846 0.176 Total Gray Vol 537116.03 49237.082 605387.50 52872.974 $<0.0001^{*}$ Supratentorial Vol Not Vent 890593.90 91466.531 931750.57 1000702.988 0.102 Suprat | CC Posterior | | 915.380007 | 154./40968/ | 993.586667 | 242.0204174 | 0.141 |
| CC Central 397.420000 71.6994/53 477.070000 134.5873/49 0.006* CC Mid Anterior 374.936667 59.8676557 473.610000 123.3682806 <0.0001* | CC Mid Posterior | | 415./13333 | 108.1424818 | 527.516667 | 138./833839 | 0.001* |
| CC Mid Anterior $3/4.936667$ 59.8676577 $4/3.610000$ 123.3682806 $<0.0001^*$ CC Anterior 838.180000 162.7772995 903.726667 219.2479370 0.194 Brain Seg Vol1057036.83 106927.656 1096200.10 109800.967 0.167 Brain Seg VolNot 1008581.90 97810.849 1063550.63 109526.233 $0.045*$ Brain Seg VolNot 1008120.60 97739.058 1063076.47 109351.359 $0.045*$ (Left) Lh Cortex Vol 194036.83 21119.643 222046.67 21432.283 $<0.0001*$ (Right) Rh Cortex Vol 193918.67 19926.848 224365.57 20586.643 $<0.0001*$ Cortex Vol 387955.50 40807.923 446412.13 41589.586 $<0.0001*$ LhCerebral White 224764.17 28654.251 215306.07 29886.351 0.216 Matter Vol224324.47 25912.423 213984.03 30639.288 0.163 Cerebral White 224324.47 25912.423 213984.03 30639.288 0.163 Sub Cort Gray Vol 51088.07 5618.180 53040.20 5413.846 0.176 Supratentorial Vol 933436.97 100192.717 961176.07 100703.482 0.289 Supratentorial Vol Not Vent 890593.90 91466.531 931750.57 100072.998 0.102 Supratentorial Vol Not Vent 890593.90 91466.531 931750.57 100072.998 0.102 Supra ten | CC Central | | 397.420000 | /1.6994/53 | 477.070000 | 134.58/3/49 | 0.006* |
| CC Anterior $838,180000$ $162,77/2995$ $903,726667$ $219,2479370$ 0.194 Brain Seg Vol1057036.83 106927.656 1096200.10 109800.967 0.167 Brain Seg VolNot 1008581.900 97810.849 1063550.63 109526.233 $0.045*$ Brain Seg VolNot 1008120.600 97739.058 1063076.47 109351.359 $0.045*$ (Left) Lh Cortex Vol 194036.83 21119.643 222046.67 21432.283 $<0.0001*$ (Right) Rh Cortex Vol 193918.67 19926.848 224365.57 20586.643 $<0.0001*$ Cortex Vol 387955.50 40807.923 446412.13 41589.586 $<0.0001*$ LhCerebral White 224764.17 28654.251 215306.07 29886.351 0.216 Matter Vol449088.50 54198.588 429290.17 60405.048 0.187 Sub Cort Gray Vol 51088.07 5618.180 53040.20 5413.846 0.176 Total Gray Vol 537116.03 4927.082 605387.50 52872.974 $<0.0001*$ Supratentorial Vol Not Vent 890593.90 91466.531 931750.57 100072.998 0.102 Supra Tentorial Vol Not Vent Vox 888444.57 91399.856 929328.70 99565.359 0.103 Mask Vol 1507750.67 152754.360 1549333.33 148809.838 0.290 Brain Seg Vol to eTIV 0.689331 0.035275 0.736909 0.0523923 $<0.0001*$ Lh Surface H | CC Mid Anterior | | 3/4.93666/ | 59.86/655/ | 4/3.610000 | 123.3682806 | <0.0001* |
| Brain Seg Vol105/036.83106927.6561096200.10109800.9670.167Brain Seg VolNot1008581.9097810.8491063550.63109526.2330.045*Vent SurfNot1008120.6097739.0581063076.47109351.3590.045*(Left)Lh Cortex Vol194036.8321119.643222046.6721432.283<0.0001* | CC Anterior | | 838.180000 | 162.7772995 | 903.726667 | 219.24/93/0 | 0.194 |
| Brain Seg Vol VentNot1008581.9097810.8491063550.63109526.2330.045*Brain Seg VolNot1008120.6097739.0581063076.47109351.3590.045*(Left)Lh Cortex Vol194036.8321119.643222046.6721432.283<0.0001* | Brain Seg Vol | NT / | 105/036.83 | 106927.656 | 1096200.10 | 109800.967 | 0.16/ |
| Brain Seg Vol Vent SurfNot1008120.6097739.0581063076.47109351.3590.045*(Left)Lh Cortex Vol194036.8321119.643222046.6721432.283<0.0001* | Brain Seg Vol Vent | Not | 1008581.90 | 97810.849 | 1063550.63 | 109526.233 | 0.045* |
| Vent Suri (Left)Lh Cortex Vol194036.8321119.643222046.6721432.283<0.0001*(Right) Rh Cortex Vol193918.6719926.848224365.5720586.643<0.0001* | Brain Seg Vol | Not | 1008120.60 | 97739.058 | 1063076.47 | 109351.359 | 0.045* |
| (Left)Lh Cortex Vol194036.8521119.043222046.6721432.285<0.0001*(Right) Rh Cortex Vol193918.6719926.848224365.5720586.643<0.0001* | Vent Sun (Left) Lh Center Vel | | 104026 92 | 21110 642 | 222046 67 | 01420 002 | -0.0001* |
| (Right) Rn Cortex Vol193918.6719926.848224305.5720386.043<0.0001*Cortex Vol387955.5040807.923446412.1341589.586<0.0001* | (Left)Lft Cortex Vol | | 194030.83 | 21119.045 | 222040.07 | 21432.283 | <0.0001* |
| Cortex Vol387955.5040807.923446412.1341589.586<0.0001*LhCerebralWhite224764.1728654.251215306.0729886.3510.216RhCerebralWhite224324.4725912.423213984.0330639.2880.163CerebralWhite Matter Vol449088.5054198.588429290.1760405.0480.187Sub Cort Gray Vol51088.075618.18053040.205413.8460.176Total Gray Vol537116.0349237.082605387.5052872.974<0.0001* | (Right) Rh Cortex Vol | | 193918.07 | 19920.848 | 224303.37 | 20380.043 | <0.0001* |
| LnCerebralwhite224764.1728654.251215306.0729886.3510.216Matter Vol224324.4725912.423213984.0330639.2880.163Matter Vol449088.5054198.588429290.1760405.0480.187Cerebral White Matter Vol449088.5054198.588429290.1760405.0480.187Sub Cort Gray Vol51088.075618.18053040.205413.8460.176Total Gray Vol537116.0349237.082605387.5052872.974<0.0001* | Cortex Vol | | 38/955.50 | 40807.923 | 446412.13 | 41589.586 | <0.0001* |
| Natter VolRhCerebralWhite224324.4725912.423213984.0330639.2880.163Matter Vol449088.5054198.588429290.1760405.0480.187Sub Cort Gray Vol51088.075618.18053040.205413.8460.176Total Gray Vol537116.0349237.082605387.5052872.974<0.0001* | Ln Cerebral white | | 224764.17 | 28654.251 | 215306.07 | 29886.351 | 0.216 |
| RhCerebralWrite224324.4725912.423213984.0330639.2880.163Matter Vol449088.5054198.588429290.1760405.0480.187Sub Cort Gray Vol51088.075618.18053040.205413.8460.176Total Gray Vol537116.0349237.082605387.5052872.974<0.0001* | Dh Carabral White | | | | | | |
| Cerebral White Matter Vol 449088.50 54198.588 429290.17 60405.048 0.187 Sub Cort Gray Vol 51088.07 5618.180 53040.20 5413.846 0.176 Total Gray Vol 537116.03 49237.082 605387.50 52872.974 $<0.0001*$ Supratentorial Vol 933436.97 100192.717 961176.07 100703.482 0.289 Supratentorial Vol Not Vent 890593.90 91466.531 931750.57 100072.998 0.102 Supra Tentorial Vol Not Vent Vox 888444.57 91399.856 929328.70 99565.359 0.103 Mask Vol 1507750.67 152754.360 1549333.33 148809.838 0.290 Brain Seg Vol to eTIV 0.689331 0.0335275 0.736909 0.0523923 $<0.0001*$ Lh Surface Holes 42.57 44.634 80.70 56.292 $0.005*$ Surface Holes 82.57 81.250 152.97 102.704 $0.005*$ | Matter Vol | | 224324.47 | 25912.423 | 213984.03 | 30639.288 | 0.163 |
| Sub Cort Gray Vol51088.075618.18053040.205413.8460.176Total Gray Vol537116.0349237.082605387.5052872.974<0.0001* | Cerebral White Matter Vol | | 449088.50 | 54198.588 | 429290.17 | 60405.048 | 0.187 |
| Total Gray Vol537116.0349237.082605387.5052872.974<0.0001*Supratentorial Vol933436.97100192.717961176.07100703.4820.289Supratentorial Vol Not Vent890593.9091466.531931750.57100072.9980.102Supra Tentorial Vol Not Vent Vox888444.5791399.856929328.7099565.3590.103Mask Vol1507750.67152754.3601549333.33148809.8380.290Brain Seg Vol to eTIV0.6893310.03352750.7369090.0523923<0.0001* | Sub Cort Gray Vol | | 51088.07 | 5618.180 | 53040.20 | 5413.846 | 0.176 |
| Supratentorial Vol933436.97100192.717961176.07100703.4820.289Supratentorial Vol Not Vent890593.9091466.531931750.57100072.9980.102Supra Tentorial Vol Not Vent Vox888444.5791399.856929328.7099565.3590.103Mask Vol1507750.67152754.3601549333.33148809.8380.290Brain Seg Vol to eTIV0.6893310.03352750.7369090.0523923<0.0001* | Total Gray Vol | | 537116.03 | 49237.082 | 605387.50 | 52872.974 | < 0.0001* |
| SupratentorialVol Not Vent890593.9091466.531931750.57100072.9980.102Supra Tentorial Vol Not Vent Vox888444.5791399.856929328.7099565.3590.103Mask Vol1507750.67152754.3601549333.33148809.8380.290Brain Seg Vol to eTIV0.6893310.03352750.7369090.0523923<0.0001* | Supratentorial Vol | | 933436.97 | 100192.717 | 961176.07 | 100703.482 | 0.289 |
| Supra Tentorial Vol Not Vent Vox888444.5791399.856929328.7099565.3590.103Mask Vol1507750.67152754.3601549333.33148809.8380.290Brain Seg Vol to eTIV0.6893310.03352750.7369090.0523923<0.0001* | Supratentorial Vol Not Vent | | 890593.90 | 91466.531 | 931750.57 | 100072.998 | 0.102 |
| Mask Vol1507750.67152754.3601549333.33148809.8380.290Brain Seg Vol to eTIV0.6893310.03352750.7369090.0523923<0.0001* | Supra Tentorial Vol Not Vent Vox | | 888444.57 | 91399.856 | 929328.70 | 99565.359 | 0.103 |
| Brain Seg Vol to eTIV0.6893310.03352750.7369090.0523923<0.0001*Lh Surface Holes42.5744.63480.7056.2920.005*Surface Holes82.5781.250152.97102.7040.005* | Mask Vol | | 1507750.67 | 152754.360 | 1549333.33 | 148809.838 | 0.290 |
| Lh Surface Holes42.5744.63480.7056.2920.005*Surface Holes82.5781.250152.97102.7040.005* | Brain Seg Vol to eTIV | | 0.689331 | 0.0335275 | 0.736909 | 0.0523923 | < 0.0001* |
| Surface Holes 82.57 81.250 152.97 102.704 0.005* | Lh Surface Holes | | 42.57 | 44.634 | 80.70 | 56.292 | 0.005* |
| | Surface Holes | | 82.57 | 81.250 | 152.97 | 102.704 | 0.005* |

*: statistically significant as p value < 0.05

| Left cortex segments | Patients | • | Controls | | P value |
|-----------------------------------|----------|-----------|----------|-----------|----------|
| volumes | Mean | Std. | Mean | Std. | |
| | | Deviation | | Deviation | |
| left banks of superior temporal | 1954.57 | 428.32 | 2116.70 | 532.52 | 0.20 |
| sulcus (bankssts) volume | | | | | |
| left caudal anterior cingulate | 1482.30 | 458.72 | 1604.80 | 447.51 | 0.30 |
| volume | | | | | |
| left caudal middle frontal | 4883.20 | 999.11 | 5900.03 | 1075.83 | < 0.001* |
| volume | | | | | |
| left cuneus volume | 2441.33 | 369.67 | 3024.70 | 553.26 | <0.001* |
| left entorhinal volume | 2038.17 | 370.51 | 2037.73 | 418.40 | 1.00 |
| left fusiform volume | 8421.37 | 1149.11 | 9051.93 | 1689.25 | 0.10 |
| left inferior parietal volume | 9561.03 | 1341.31 | 11257.80 | 1580.05 | <0.001* |
| left inferior temporal volume | 9866.80 | 1479.09 | 10511.80 | 1647.82 | 0.12 |
| left isthmus cingulate volume | 2275.47 | 348.65 | 2500.40 | 428.87 | 0.03* |
| left lateral occipital volume | 9719.67 | 1385.12 | 11702.73 | 1585.44 | <0.001* |
| left lateral orbitofrontal volume | 6688.83 | 952.40 | 7296.60 | 702.62 | 0.01* |
| left lingual volume | 5308.90 | 888.71 | 6428.57 | 1387.85 | < 0.001* |
| left medial orbitofrontal | 4418.47 | 582.46 | 4731.57 | 716.54 | 0.07 |
| volume | | | | | |
| left middle temporal volume | 9213.73 | 1622.96 | 9948.80 | 1687.72 | 0.09 |
| left Para hippocampal volume | 1959.77 | 284.71 | 2056.10 | 361.33 | 0.26 |
| left paracentral volume | 2953.83 | 479.99 | 3332.83 | 419.77 | < 0.001* |
| left parsopercularis volume | 3722.10 | 652.56 | 4316.43 | 561.76 | < 0.001* |
| left parsorbitalis volume | 2036.60 | 381.95 | 2230.37 | 307.60 | 0.03* |
| left parstriangularis volume | 2977.20 | 544.27 | 3409.10 | 467.40 | < 0.001* |
| left pericalcarine volume | 1572.80 | 348.52 | 2197.40 | 616.93 | < 0.001* |
| left postcentral volume | 7472.57 | 1061.14 | 9546.90 | 1438.95 | < 0.001* |
| left posterior cingulate volume | 2646.43 | 461.39 | 2896.30 | 378.97 | 0.03* |
| left precentral volume | 10659.17 | 1274.61 | 12887.27 | 1213.57 | < 0.001* |
| left precuneus volume | 7752.20 | 1209.85 | 9145.37 | 1166.61 | < 0.001* |
| left rostral anterior cingulate | 2248.47 | 492.90 | 2394.73 | 636.33 | 0.32 |
| volume | | | | | |
| left rostral middle frontal | 12004.57 | 2200.85 | 14052.40 | 2306.23 | < 0.001* |
| volume | | | | | |
| left superior frontal volume | 18525.83 | 2244.29 | 20681.67 | 3263.34 | < 0.001* |
| left superior parietal volume | 10259.03 | 1809.63 | 12702.73 | 1744.37 | < 0.001* |
| left superior temporal volume | 10292.63 | 1617.00 | 11242.20 | 1270.40 | 0.01* |
| left supramarginal volume | 8950.80 | 1436.85 | 10549.03 | 1945.79 | < 0.001* |
| left frontal pole volume | 794.30 | 118.76 | 876.87 | 253.30 | 0.11 |
| left temporal pole volume | 2267.97 | 499.77 | 2187.63 | 494.67 | 0.53 |
| left transverse temporal volume | 858.10 | 234.06 | 1096.40 | 183.21 | < 0.001* |
| left insula volume | 6566.67 | 965.65 | 6921.73 | 630.58 | 0.10 |

 Table 4: Left cortex segments volumes in patients and controls.

 ft cortex segments
 Patients
 Controls

*: statistically significant as *p* value < 0.05

1008581.90

97810.85

1063550.63 109526.23

0.04*

Brain Seg Vol Not Vent

| Dight cortex segments volumes Detients Controls Detients | | | | | P voluo |
|---|-------------------|-----------|------------|------------|-----------|
| Right cortex segments volumes | r attents Moon | Sta | Controls | Std | r value |
| | Wiean | Deviation | Wiean | Deviation | |
| Right banks of superior temporal sulcus | 1735.97 | 290.533 | 2082.83 | 354.334 | < 0.0001* |
| (bankssts) volume | 1,000,7 | 2701000 | 2002.00 | | (010001 |
| Right caudal anterior cingulate volume | 1647.90 | 345.039 | 2017.07 | 865.274 | 0.034* |
| Right caudal middle frontal volume | 4612.33 | 939.113 | 5344.60 | 1095.393 | 0.007* |
| Right cuneus volume | 2700.87 | 367.458 | 3348.07 | 723.128 | < 0.0001* |
| Right entorhinal volume | 2077.67 | 423.555 | 1942.40 | 511.092 | 0.269 |
| Right fusiform volume | 8629.20 | 1161.083 | 9292.57 | 1305.319 | 0.042* |
| Right inferior parietal volume | 12027.47 | 1959.123 | 13655.83 | 2010.291 | 0.002* |
| Right inferior temporal volume | 9458.57 | 1541.034 | 9828.60 | 1965.242 | 0.420 |
| Right isthmus cingulate volume | 2050.63 | 319.781 | 2404.63 | 409.949 | < 0.0001* |
| Right lateral occipital volume | 10195.00 | 1487.188 | 12446.43 | 1979.134 | < 0.0001* |
| Right lateral orbitofrontal volume | 6604.20 | 861.793 | 7139.90 | 763.446 | 0.013* |
| Right lingual volume | 5609.60 | 875.345 | 6959.00 | 1180.034 | < 0.0001* |
| Right medial orbitofrontal volume | 4752.37 | 731.052 | 5257.87 | 576.049 | 0.004* |
| Right middle temporal volume | 9926.87 | 1086.369 | 11133.30 | 1579.690 | 0.001* |
| Right parahippocampal volume | 1853.80 | 279.402 | 1882.17 | 199.258 | 0.652 |
| Right paracentral volume | 3186.37 | 410.212 | 3718.93 | 439.307 | < 0.0001* |
| Right parsopercularis volume | 3023.20 | 501.865 | 3672.27 | 395.282 | < 0.0001* |
| Right parsorbitalis volume | 2337.13 | 258.530 | 2656.93 | 335.407 | <0.0001* |
| Right parstriangularis volume | 3288.13 | 525.776 | 3903.80 | 670.673 | < 0.0001* |
| Right pericalcarine volume | 1773.07 | 363.888 | 2526.63 | 690.421 | < 0.0001* |
| Right postcentral volume | 7069.37 | 1077.314 | 9084.83 | 1417.072 | < 0.0001* |
| Right posteriorcingulate volume | 2654.17 | 418.981 | 3081.77 | 575.604 | 0.002* |
| Right precentral volume | 10206.83 | 1212.327 | 12495.47 | 1324.692 | < 0.0001* |
| right precuneus volume | 7939.20 | 1199.400 | 9390.73 | 1261.145 | < 0.0001* |
| Right rostral anterior cingulate volume | 1638.47 | 304.272 | 1897.13 | 371.335 | 0.005* |
| Right rostral middle frontal volume | 12421.83 | 1979.083 | 14688.83 | 1890.483 | <0.0001* |
| Right superior frontal volume | 17419.50 | 2587.436 | 19818.13 | 2748.135 | 0.001* |
| Right superior parietal volume | 9998.07 | 1526.943 | 12047.50 | 1810.583 | <0.0001* |
| Right superior Temporal volume | 9397.90 | 1139.094 | 10723.43 | 1002.214 | < 0.0001* |
| Right supramarginal volume | 7720.63 | 1087.844 | 9712.17 | 1478.361 | < 0.0001* |
| Right frontal pole volume | 947.33 | 139.026 | 1011.70 | 213.638 | 0.172 |
| Right temporal pole volume | 2429.33 | 418.308 | 2299.10 | 512.666 | 0.285 |
| Right transverse Temporal volume | 608.37 | 121.987 | 867.03 | 121.772 | <0.0001* |
| Right insula volume | 6413.77 | 950.493 | 6830.23 | 806.571 | 0.072 |
| Brain Seg Vol Not Vent | 1008581.90 | 97810.849 | 1063550.63 | 109526.233 | 0.045* |

Table 5: Right cortex segments volumes in patients and controls

*: statistically significant as *p* value <0.05

Patients showed significant reductions in right banks of superior temporal sulcus (bankssts), caudal middle frontal, fusiform, and cuneus volumes compared to controls (p < 0.0001). However, there were no significant differences in right entorhinal, right inferior temporal, or right inferior parietal volume. Patients also had a significant reduction in the right inferior parietal volume compared to controls (p = 0.002).

The right isthmus cingulate volume was significantly reduced in patients compared to controls (p < 0.0001). The right lateral occipital volume also exhibited a significant difference. Further significant differences were evident in the right lateral orbitofrontal volume. The right lingual volume was significantly lower in patients than in controls (p < 0.0001). The right medial orbitofrontal volume also showed significant differences (p = 0.004). The right middle temporal volume was significantly reduced in patients compared to controls (p = 0.001). The right pars triangularis volume showed a significant reduction in patients compared to controls (p <0.0001). The right pericalcarine volume was significantly lower in patients than in controls (p < 0.0001). The right postcentral volume also exhibited significant differences (p <0.0001). The right posterior cingulate volume was significantly reduced in patients compared to controls (p =0.002). The right percentage in patients was significantly lower than controls (p < 0.0001). The right precuneus volume showed significant differences as well (p < 0.0001). The right rostral cingulate anterior volume was significantly reduced in patients compared to controls (p = 0.005). The right rostral middle frontal volume showed significant differences (p < p)0.0001).

The right superior frontal volume was significantly lower in patients than in controls (p = 0.001). The right superior parietal volume also exhibited significant differences (p < 0.0001). The right superior temporal volume was significantly reduced in patients compared to controls (p < 0.0001). The supramarginal volume also right showed significant differences (p < p)0.0001). Finally, the right transverse temporal volume was significantly reduced in patients compared to controls (p < 0.0001). The analysis revealed significant reductions in regions cortical in patients. highlighting the impact of underlying conditions on brain morphology, also BrainSegVolNotVent showed the significant differences (p = 0.045). Table 5

A significant negative correlation was found between brain volume and Fazekas scores (r = -0.65, P < 0.01), suggesting that higher WMH severity is associated with reduced GMV. Also, a significant positive correlation between brain volume and cognitive scores suggest that larger brain volumes are associated with better cognitive performance. **Table 6**

Table 6: Correlation between brain volume and Fazekas score and between brain volume and cognitive scores.

| Variable | r | P value |
|------------------------|---------|-----------|
| Fazekas Score (0-6) | -0.65** | p < 0.01* |
| Cognitive Score (0-30) | 0.74** | p < 0.01* |

*: statistically significant as *p* value <0.05

Cases

Case 1: A 60-year-old female patient presented with normal clinical data and normal cognition. (Figure 1)

Case 2: A 65-year-old female patient had diabetes mellitus for 20 years, complaining of mild cognitive impairment._complaining of mild cognitive impairment. (Figure 2) Case 3: A 75-year-old male patient had hypertension and was a heavy smoker for 50 years, (Figure 3)

Case 4: A 77-year-old male patient complaining of mild cognitive impairment. (Figure 4)

Case 5: A 65-year-old male patient had hypertension and complaining of moderate cognitive impairment and unsteady gait. (Figure 5)

<u>Case (1)</u> A 60-year-old female patient presented with normal clinical data and normal cognition.



Figure 1: Brain MRI images (A) T1 axial, (B) T1 sagittal, (C) T1 coronal, (D, E, F) Cortical and subcortical structures regional reconstruction and segmentation using the Free Surfer image analysis suite v6. Findings: Normal Brain MRI (Fazekas score 0). Estimated total intracranial volume: 1568142.875.

A 65-year-old female patient had diabetes mellitus for 20 years, complaining of mild cognitive impairment.









Figure 2: Brain MRI images (A) T2 axial, (B) T1 sagittal, (C) FLAIR axial, (D) T1 coronal, (E, F, G) Cortical and subcortical structures regional reconstruction and segmentation using the FreeSurfer image analysis suite v6. Findings: WMHs are seen periventricular and deep white matter (Fazekas score 6). Estimated total intracranial volume: 1497770

Case (3)

A 75-year-old male patient had hypertension and was a heavy smoker for 50 years, complaining of mild cognitive impairment.



Figure 3: Brain MRI images (A) T2 axial, (B) T1 sagittal, (C) FLAIR axial, (D) T1 coronal, (E, F, G) Cortical and subcortical structures regional reconstruction and segmentation using the FreeSurfer image analysis suite v6. Findings: WMHs are seen periventricular and as deep white matter (Fazekas score 3). Estimated total intracranial volume: 1382510.

Case (4) A 77-year-old male patient complaining of mild cognitive impairment.









Figure 4: Brain MRI images (A) T2 coronal, (B) T1 sagittal, (C, D) FLAIR axial, (E, F, G) Cortical and structures subcortical regional reconstruction and segmentation using the FreeSurfer image analysis suite Findings: WMHs are seen v6. periventricular and at deep white matter (Fazekas score 6). Estimated total intracranial volume: 1553660.



Case (5)

A 65-year-old male patient had hypertension and complaining of moderate cognitive impairment and unsteady gait.



Figure 5: Brain MRI images (A) T2 axial, (B) T1 sagittal, (C) FLAIR axial, (D) SWI axial, (E, F, G) Cortical subcortical and structures regional reconstruction and segmentation using the FreeSurfer image analysis suite v6. Findings: WMHs are seen periventricular and at deep white matter with infarctions lacunar and micro bleeds (Fazekas score Estimated 6). total intracranial volume: 1710890.

Discussion

Cerebral small vessel disease (CSVD) is a prevalent vascular condition associated with aging, characterized by lesions in the brain's small penetrating arteries. It is often linked to cognitive decline. particularly affecting executive functions and memory. A key feature of CSVD is WMHs detectable via neuroimaging ^[15]. This study aimed to analyze cortical atrophy patterns in ACSVD by examining GMV variations in relation to WMH severity, as graded by the Fazekas scale, and to assess correlations between GMV and cognitive impairment and it revealed significant GMV reductions in ACSVD patients, particularly in regions associated with cognitive functions.

This prospective study involved 100 patients diagnosed with ACSVD via conventional MRI, focusing on WMH presence and excluding non-lacunar infarctions. The patient cohort was compared to 50 healthy controls matched for age and sex. Cognitive status was classified into normal cognition (NC) and mild cognitive impairment (MCI). The patient group was significantly older than controls, aligning with research indicating that aging exacerbates cognitive impairments and ACSVD development ^[16].

Higher Fazekas scores in patients indicated more severe white matter changes, correlating negatively with brain volume, consistent with literature by Wu Y et al, linking WMH severity to cognitive decline. Significant findings included enlarged left lateral and inferior lateral ventricles in patients compared to controls, correlating with cognitive decline. However, some studies suggested that ventricular enlargement may not always directly correlate with cognitive impairment. Cerebellar atrophy was observed, with reduced left cerebellum white matter and cortex volumes in patients, consistent with findings linking cerebellar atrophy to cognitive deficits. The left thalamus and caudate showed non-significant differences, while the left putamen had similar volumes groups, reflecting variability in across subcortical structure atrophy^[16].

In the current study, the third and fourth ventricles were significantly larger in patients, aligning with research connecting ventricular enlargement to WMH severity. The left hippocampus and amygdala volumes were significantly reduced in patients, with higher CSF volumes observed, supporting the importance of hippocampal volume in predicting cognitive outcomes. The right lateral ventricle was also significantly larger in patients, while the right inferior lateral ventricle showed no significant difference. Notably, the right cerebellum white matter was significantly reduced in patients. reinforcing the association between lateral ventricular enlargement and cognitive decline. Overall, significant structural changes were noted in patients, particularly in regions associated with cognitive and motor functions, aligning with studies indicating that GMV loss correlates with cognitive deficits in ACSVD. The left bankssts and caudal anterior cingulate volumes showed no significant differences, suggesting relative preservation in these areas. while the left Caudal middle frontal volume exhibited significant atrophy, correlating with observed cognitive deficits.

Our study aligns with study by Tuladhar et al. ^[1V] who found that increased WMH burden disrupts cortical-subcortical networks, leading to cognitive deficits. Higher WMH burden was associated with reduced GMV in frontotemporal areas, but increased GMV in paracentral regions.

The left Cuneus volume in the current study showed significant differences, indicating potential visual processing impairments, while the left Entorhinal volume remained stable, suggesting some regions may not be affected by ACSVD. According to Wang et al. ^[18], the left Inferior parietal volume showed significant atrophy, potentially impacting spatial awareness and attention aligning with this study. The left Inferior temporal volume indicated a nonsignificant decline, while the left Isthmus cingulate volume showed significant changes, correlating with mood disorders. Brain regions revealing significant variations in GMV between patients and control groups were widely distributed across the brain. Patients with elevated WMH scores displayed reduced GMV in specific subregions of the frontal and temporal lobes, as well as in the para hippocampal hippocampus, gyrus, and Notably, thalamus. the GMV in the ventrolateral area of the right inferior temporal gyrus, along with the right posterior parietal and occipital thalamus, illustrated a positive correlation with Montreal Cognitive Assessment scores. GMV in the extreme ventrolateral area of right inferior temporal gyrus along with the entorhinal cortex of left para hippocampal gyrus were positively correlated with both Montreal Cognitive Assessment and Mini-Mental Status Examination scores.

Significant reductions were observed in the left lateral occipital, Lateral orbitofrontal, Lingual, and Medial orbitofrontal volumes, indicating potential deficits in visual processing, decision-making, and emotional regulation.

This study is in line with previous research by Wang et al as the left Middle temporal volume reduced significantly, while the left Para hippocampal volume indicated no significant difference, suggesting preservation in memory encoding functions also the left Paracentral and Pars opercularis volumes showed significant reductions, indicating potential impacts on motor control and language processing. ^[18].

This study and Caruso P et al, found that CSVD is increasingly recognized as a significant contributor to cognitive decline, particularly among the aging population, characterized by lesions in the small penetrating arteries of the brain, CSVD manifests through various neuroimaging findings, most notably WMHs visible on MRI scans. These hyperintensities are associated with disruptions in neural connectivity, leading to deficits in executive functions, memory, and overall cognitive performance [19].

In summary, this study investigates the complex relationship between WMHs and GMV in patients with ACSVD. The significant atrophy observed across various brain regions correlates with cognitive decline, emphasizing the need to consider both structural and functional aspects of neurodegeneration. As ACSVD prevalence with increases aging populations, understanding its cognitive health impact is crucial for developing targeted interventions and improving patient outcomes. Continued exploration into the mechanisms underlying cognitive decline in small vessel disease is essential for informing clinical practices and guiding therapeutic strategies aimed at preserving cognitive health in aging populations.

Limitations of the study: WMH grading relied on the Fazekas scale, which, despite good inter-rater reliability, remains a semiquantitative measure. Future studies should incorporate automated lesion segmentation techniques to enhance accuracy and reproducibility of WMH quantification.

Conclusion

This study underscores the impact of WMHrelated GMV reductions on cognitive impairment in ACSVD and highlights the potential role of advanced neuroimaging for early detection and intervention.

The observed reductions in specific brain regions, particularly those implicated in cognitive functions, suggest a complex interplay between vascular pathology and cognitive outcomes. While some regions demonstrated resilience, others showed pronounced atrophy that correlates with cognitive deficits. These results highlight the necessity for a multidimensional approach in assessing cognitive impairment in ACSVD patients, considering individual variability and the potential for compensatory mechanisms. Future research should aim to further clarify these relationships and explore interventions that may mitigate cognitive decline in this vulnerable population.

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