A Pilot Study for Investigating Differences between Alzheimer's Patients with and without Significant Vascular Pathology

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Abstract— **Distinguishing Alzheimer's disease (AD) from mixed Alzheimer's and vascular dementia (VD) is a challenging task. In this study, we explored the differences between AD patients and a group with a mixed pathology of AD with cerebrovascular disease (CVD) by analyzing the volumes of several brain regions vulnerable to AD and evidenced by white matter hyper-intensities (WMHs). Moreover, we investigated the correlation between brain volumes and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores of the AD and AD-CVD groups. We collected T1-weighted Magnetization Prepared Acquisition with Gradient Echo (MPRAGE) MRI scans from 9 AD participants and 8 AD-CVD participants. Then, we performed the region of interest (ROI) analysis over the MRI data to measure the gray matter (GM) volume of the hippocampus, frontal gyrus, and precuneus as well as the cerebrospinal fluid (CSF) volume of ventricles. Also, we calculated the volume of white matter hyper-intensities (WMHs) of the whole brain and of the frontal-temporal (FT) area. The results did not show any correlation between the baseline ADAS-Cog scores of AD participants and their volumes of above-affected areas and WMHs, while in the AD-CVD group, the CSF volume in ventricles showed a high correlation with ADAS-Cog scores (Spearman's ρ = 0.714). We did not observe any statistically significant difference in these volumes between AD patients and AD-CVD group.**

Keywords— **Alzheimer's disease (AD), Cerebrovascular disease (CVD), Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog), Magnetic resonance imaging (MRI), White matter hyper-intensities.**

I. Introduction

Alzheimer's disease (AD) is considered a neurodegenerative disorder that impairs one's functional, cognitive, and behavioral activities [1]. For measuring the severity of AD, a standard cognitive assessment tool, called Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [2] is commonly used, in which the AD patients are provided with 11 specific tasks and receive a score in the range of 0 to 70, where higher ADAS-Cog scores indicate more impairment [3]. Magnetic Resonance Imaging (MRI) is also commonly utilized to detect the atrophy of an Alzheimer's brain. Previous MRI studies on AD reported the gray matter (GM) volume changes of several brain areas, including the hippocampus, frontal cortex, precuneus as well as the cerebrospinal fluid (CSF) volume changes in ventricles [4–7]. Besides, the pathological alterations in white matter (WM), particularly demyelination, have been reported to happen in the early stage of Alzheimer's brain [8]. The alternations of water content in the WM structures are characterized as white matter hyperintensities (WMHs) [9]. WMHs are related to vascular pathology and have a significant effect on cognitive deficits [9]. They are found in the MRI scans of AD, those with vascular dementia (VD) as well as aging individuals [9, 10]. In this pilot study, we investigated the plausible correlations of brain volume and WMHs among AD patients and a group with the mixed pathology of AD with cerebrovascular disease (CVD); moreover, we investigated the correlation of the brain volume and the severity of the disease using the ADAS-Cog scores.

Severe CVD is seen in vascular dementia (VD). VD occurs due to the weakened blood flow in our brain, which impairs the processes such as logical thinking, cognition, memory [11]. VD is primarily distinguished from AD by estimating the Hachinski Ischemic Score (HIS) scale [12, 13], in which thirteen factors, including the history of stroke, depression, hypertension, are considered for scoring the patients. VD is also characterized by the existence of excessive WMHs in MRI data [9, 14]. The risk factors of VD, are also frequently noticed in AD, particularly those with cardiovascular disease [12]. Several studies have reported an overlap between AD and VD pathologies [12, 15], making the differential diagnosis challenging [16]. For that reason, in case of the co-occurrence of AD and VD pathologies, the patients are diagnosed as mixed AD and VD [12]. VD patients have acute CVD; herein, we referred to the mixed pathology of AD and VD as AD-CVD and defined it as AD with significant CVD meeting both the National Institute of Neurological Disorder and Stroke's definition of AD with CVD and having a HIS score between 4 and 7.

The goal of this pilot study was to: 1) compare the brain volumes and WMHs of AD and AD-CVD; and 2) investigate the correlation of AD and AD-CVD groups and their corresponding ADAS-Cog scores as a measure of their severity.

II. Methodology

Data for this study have been adopted from a current clinical trial [17, 18]. In this pilot study, we included 9 participants with AD and 8 with AD-CVD. All patients' diagnoses have been based on a neurologist or psychiatrist's clinical diagnosis along with using brain imaging scans and applying HIS scores.

The demographic characteristics and baseline ADAS-Cog scores of the participants are listed in Table 1. All the participants underwent 3T MRI scanning. From the participants, we collected T1-weighted MPRAGE MRI data with repetition time, TR = 1800 ms, echo time, TE = 2.93 ms, inversion time, TI = 900 ms, field of view matrix = 256 × 256, spatial resolution = 1 mm, and time of acquisition = 5:46 min. For segmentation of the MRI data, we used CAT12 (Computational Anatomy Toolbox, ver 12.6, expert mode, http://www.neuro.uni-jena.de/cat/) [19] with SPM12 (Statistical Parametric Mapping software, ver 7487, https://www.fil.ion.ucl.ac.uk/spm/) in MATLAB (ver 2018b). We manually checked the image and preprocessing qualities (resolution, noise, and bias) of all MRI data from their CAT12 reports to ensure that they had almost the same image quality ratings. Using CAT12 in expert mode, the MRI data were segmented into GM, WM, CSF, WMHs tissue maps, and we estimated their native space volumes. Although the WMHs are usually segmented from the Fluid-Attenuated Inversion Recovery sequence of MRI data, a cross-validation study has been done in CAT12 for segmenting WMHs using only T1-weighted MRI data [20]. For calculating WMHs volume in the frontal-temporal (FT) region, we created two masks of the frontal and temporal areas of the brain using the xjView toolbox (https://www.alivelearn.net/xjview/) in avg152T1 atlas target. We then added them by ImCalc function of SPM12 to make a single mask of the FT region. Later, we resliced this mask with the segmented WMHs image to calculate WMHs volume in the FT region by multiplying the number of voxels with its voxel size. In the CAT12 batch program, we also used the Neuromorphometrics brain atlas to perform an ROI-based analysis instead of whole-brain analysis because we knew the affected regions to investigate. Neuromorphometrics brain atlas gave only CSF and GM volumes of our ROIs.

Table 1 Demographic characteristics and ADAS-Cog scores of participants

	AD *n* = 9, 7 males	AD-CVD n = 8, 6 males	Two-tailed *p*-values
Age (y), mean ± SD	71.9 ± 8.7	73.9 ± 7.5	0.80
ADAS-Cog total scores, mean ± SD	12.2 ± 4.4	13.8 ± 5.3	0.62

III. Results

A. Statistical data analysis

We ran a two-tailed Wilcoxon rank-sum test over age and ADAS-Cog scores in the AD group and AD-CVD group, where we did not observe any statistical difference between them in terms of age and sex (Table 1). We then performed Spearman's rank correlation analysis for finding the correlation of WMHs, GM in the hippocampus, MFG, SFG, precuneus, and CSF in ventricles with the ADAS-Cog scores of the AD and AD-CVD groups (Table 2). As shown, there was no significant correlation in the AD and ADAS-Cog scores, while in the AD-CVD group, ADAS-Cog scores were strongly correlated with CSF in lateral ventricles (Spearman's $\rho = 0.714$). Table 3 demonstrates the mean ± SE volumes of WMHs and regions of interest of AD and AD-CVD groups. The p-values of two-tailed Wilcoxon rank-sum test for each volume between the AD and AD-CVD group are also shown in Table 3. In our multiple comparisons, we used the Benjamini & Yekutieli technique [21] to adjust the false discovery rate at 0.05 [22]**.** Here, we observed no statistically significant difference in WMHs, GM in the hippocampus, frontal gyrus, precuneus, and CSF in the ventricles between AD patients and the AD-CVD group. Most of the volumes of the above-affected regions were similar between these two groups.

Table 2 Spearman's rank correlation coefficients (ρ) of white matter hyperintensities (WMHs) and regions of interest of the AD group and AD-CVD group with their ADAS-Cog scores. FT = Frontal-temporal, GM = Gray matter, CSF = Cerebrospinal fluid, MFG = Middle frontal gyrus, SFG = Superior frontal gyrus, L = Left, R = Right

WMHs and regions of interest	Spearman's ρ	
	ADAS-Cog scores of AD group	ADAS-Cog scores of AD-CVD group
WMHs in whole brain	0.254	0.191
WMHs in FT region	0.017	0.429
GM in hippocampus (L+R)	-0.528	0.119
CSF in lateral ventricles (L+R)	-0.068	0.714
GM in MFG (L+R)	-.0559	0.381
GM in SFG (L+R)	-0.170	0.262
GM in Precuneus (L+R)	-0.545	0.524

Table 3 Mean ± SE volumes of white matter hyperintensities (WMHs) and regions of interest of AD and AD-CVD groups. Two-tailed p-values are found after running a Wilcoxon rank-sum test between the two groups. SE = Standard error, FT = Frontal-temporal, GM = Gray matter, CSF = Cerebrospinal fluid, MFG = Middle frontal gyrus, SFG = Superior frontal gyrus, L = Left, R = Right

WMHs and regions of interest	AD mean ± SE cm^3	AD-CVD mean ± SE cm^3	Two tailed *p*-values
WMHs in whole brain	4.4 ± 1.0	6.0 ± 1.0	0.25
WMHs in FT region	2.0 ± 0.5	3.0 ± 0.6	0.14
GM in hippocampus (L+R)	4.0 ± 0.2	4.4 ± 0.2	0.46
CSF in lateral ventricles (L+R)	38.6 ± 3.3	45.9 ± 8.5	0.81
GM in MFG (L+R)	27.1 ± 1.4	28.4 ± 1.0	0.50
GM in SFG (L+R)	21.8 ± 0.7	21.8 ± 0.7	0.89
GM in Precuneus (L+R)	15.8 ± 0.5	16.6 ± 0.6	0.41

IV. Discussions

In this study, we analyzed the volumes and WMH of the brain regions that are reported to show change in AD; in particular, we calculated the GM volumes of the hippocampus, ventricles, frontal gyrus, precuneus, and CSF volume in ventricles. A reduction of GM volume is found in individuals with AD and VD [23, 24]. The hippocampus plays an important role in memory formation, and loss of it is related to both AD and VD [4, 24]. A study on 504 participants reported that AD participants have larger ventricles volume than individuals with mild cognitive issues and normal aging people [7]. The hypertrophy of the left ventricle is associated with the risk factors of the cardiovascular system and affects executive functions of the brain [25].

The atrophy of the brain, particularly in the frontal and temporal regions, occurs because of neuronal loss in the AD population [6]. The frontal lobe occupies a significant portion of the brain and is responsible for executive functions; we included volumes of the middle and superior frontal gyrus in the analysis. An imaging study also found disruption of precuneus function in the individuals with AD [5]. Here, we performed a correlation analysis over the GM volumes in hippocampus, frontal gyrus, precuneus, CSF in ventricles, and WMHs. Neither the WMHs nor the CSF of ventricles and GM volumes of ROIs were found correlated with ADAS-Cog scores of the AD group. The ROIs and WMHs volumes of AD participants may not have a significant impact on their ADAS-Cog scores at least with the patients used herein (with a clinical dementia rating of about 1). On the other hand, for the AD-CVD group, we did not observe a strong correlation between ADAS-Cog scores and brain volumes, except CSF in lateral ventricles, which is positively correlated with ADAS-Cog scores. The increase of CSF volume in lateral ventricles is usually associated with the disease severity; hence the high correlation of the ADAS-Cog scores with our AD-CVD group. However, the analysis herein is limited to select a few regions of WMHs and ROIs; other vulnerable brain regions, such as the temporal gyrus and cerebellum, should be included in future studies.

The neuropathological association between the nonvascular or vascular origins of WMHs and AD is still unclear [9]. However, vascular issues, including high blood pressure, may encourage WMHs, which contribute to the deterioration of cognitive abilities [9]. Individuals with AD-CVD might be affected more by the risk factors of WMHs compared to the AD without vascular issues. Nevertheless, most of the risk factors of AD, including smoking, high consumption of saturated fat, hypertension, are also found in VD [12]. Thus, higher values of WMHs in our AD-CVD group compared to that among AD group were expected. However, we did not observe statistically higher WMHs volume in the AD-CVD group than AD. Given that our sample size was very small, further investigations are required to verify our observations.

V. Conclusions

Our study results show no strong correlation between the tested volumes of the AD group and the severity of the condition measured by ADAS-Cog scores; in the AD-CVD group, the results showed the CSF volume in ventricles to be highly correlated with ADAS-Cog scores. We found no statistically significant difference in these volumes between the AD-CVD and AD group. However, this could be due to the small sample size of the study.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Apostolova LG (2016) Alzheimer disease. Contin Lifelong Learn Neurol 22:419–434. https://doi.org/10.1212/CON.0000000000000307
2. Kueper JK, Speechley M, Montero-Odasso M (2018) The Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog): Modifications and responsiveness in pre-dementia populations. A narrative review. J Alzheimer's Dis 63:423–444.

https://doi.org/10.3233/JAD-170991
3. Rosen WG, Mohs RC, Davis KL (1984) A new rating scale for Alzheimer's disease. Am J Psychiatry 141:1356–1364. https://doi.org/10.1176/ajp.141.11.1356
4. Schuff N, Woerner N, Boreta L, et al (2009) MRI of hippocampal volume loss in early Alzheimers disease in relation to ApoE genotype and biomarkers. Brain 132:1067–1077. https://doi.org/10.1093/brain/awp007
5. Yokoi T, Watanabe H, Yamaguchi H, et al (2018) Involvement of the precuneus/posterior cingulate cortex is significant for the development of Alzheimer's disease: A PET (THK5351, PiB) and resting fMRI study. Front Aging Neurosci 10:. https://doi.org/10.3389/fnagi.2018.00304
6. Scahill RI, Schott JM, Stevens JM, et al (2002) Mapping the evolution of regional atrophy in Alzheimer's disease: Unbiased analysis of fluid-registered serial MRI. Proc Natl Acad Sci U S A 99:4703–4707. https://doi.org/10.1073/pnas.052587399
7. Nestor SM, Rupsingh R, Borrie M, et al (2008) Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. Brain 131:2443–2454. https://doi.org/10.1093/brain/awn146
8. Sachdev PS, Zhuang L, Braidy N, Wen W (2013) Is Alzheimer's a disease of the white matter? Curr. Opin. Psychiatry 26:244–251
9. Alber J, Alladi S, Bae H-J, et al (2019) White matter hyperintensities in vascular contributions to cognitive impairment and dementia (VCID): Knowledge gaps and opportunities. Alzheimer's Dement Transl Res Clin Interv 5:107–117. https://doi.org/10.1016/j.trci.2019.02.001
10. Ramirez J, McNeely AA, Berezuk C, et al (2016) Dynamic progression of white matter hyperintensities in Alzheimer's disease and normal aging: Results from the Sunnybrook dementia study. Front Aging Neurosci 8:62. https://doi.org/10.3389/fnagi.2016.00062
11. Vascular Dementia | Symptoms & Treatments | alz.org. https://www.alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/vascular-dementia. Accessed 12 Jan 2021
12. Ravona-Springer R, Davidson M, Noy S (2003) Is the distinction between Alzheimer's disease and vascular dementia possible and relevant? Dialogues Clin. Neurosci. 5:7–15
13. Fischer P, Jellinger K, Gatterer G, Danielczyk W (1991) Prospective neuropathological validation of Hachinski's Ischaemic Score in dementias. J Neurol Neurosurg Psychiatry 54:580–583. https://doi.org/10.1136/jnnp.54.7.580
14. Kapasi A, DeCarli C, Schneider JA (2017) Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathol 134:171–186. https://doi.org/10.1007/s00401-017-1717-7
15. Snowdon DA (2003) Healthy aging and dementia: Findings from the Nun Study. Ann Intern Med 139:450–454. https://doi.org/10.7326/0003-4819-139-5_part_2-200309021-00014
16. Schneider JA, Bennett DA (2010) Where vascular meets neurodegenerative disease. In: Stroke. Lippincott Williams & Wilkins, pp S144–S146
17. Investigating the effect of repetitive transcranial magnetic stimulation (rTMS) as a treatment for Alzheimer's disease. https://clinicaltrials.gov/ct2/show/NCT02908815. Accessed 12 Jan 2021
18. Moussavi Z, Rutherford G, Lithgow B, et al (2021) Repeated transcranial magnetic stimulation for improving cognition in patients with Alzheimer disease: protocol for a randomized, double-blind, placebo-controlled trial. JMIR Res Protoc 10:e25144. https://doi.org/10.2196/25144
19. Gaser C, Dahnke R (2016) CAT-A Computational Anatomy Toolbox for the analysis of structural MRI data. HBM 2016:336–348
20. Dahnke R, Ziegler G, Gaser C (2019) Detection of white matter hyperintensities in T1 without FLAIR. In: Human Brain Mapping Conference. Rome
21. Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B 57:289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x
22. David Groppe (2021) fdr_bh - File Exchange - MATLAB Central. https://www.mathworks.com/matlabcentral/fileexchange/27418-fdr_bh. Accessed 21 Jan 2021
23. Anderson VM, Schott JM, Bartlett JW, et al (2012) Gray matter atrophy rate as a marker of disease progression in AD. Neurobiol Aging 33:1194–1202. https://doi.org/10.1016/j.neurobiolaging.2010.11.001
24. Liu C, Li C, Gui L, et al (2014) The pattern of brain gray matter impairments in patients with subcortical vascular dementia. J Neurol Sci 341:110–118. https://doi.org/10.1016/j.jns.2014.04.017
25. Restrepo C, Patel SK, Rethnam V, et al (2018) Left ventricular hypertrophy and cognitive function: A systematic review. J. Hum. Hypertens. 32:171–179

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