Correlation of regional cerebral blood flow with brain structural changes in mild cognitive impairment and Alzheimer's disease

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Abstract

Objectives

Brain atrophy and structural changes due to aging contribute strongly in the pathophysiology of mild cognitive impairment (MCI) and Alzheimer's Disease (AD). Regional cerebral blood flow (CBF) impairment is believed to be one of the initial changes in the AD continuum. In this study, we investigated the association between CBF and brain structural changes associated with aging and neurodegeneration.

Methods

Data from three groups of participants including 39 control normal (CN), 82 MCI, and 28 AD subjects were downloaded from the Alzheimer's disease Neuroimaging Initiative (ADNI). Magnetic resonance images (MRI) of participants were automatically segmented by FreeSurfer V 7.0 software and arterial spin labeling (ASL) MRI was applied to measure CBF and investigate effect of aging and structural changes on CBF in experimental groups. One way ANOVA and Pearson correlation coefficient were used to compare data and find correlation between CBF and structural changes in the brain.

Results

AD patients had significantly lower Mini-Mental State Examination (MMSE) score ($p=0.001$) and more APOE- $\epsilon 4$ carriers ($p=0.001$) as compared to the MCI and CN groups. Our findings revealed a wide spread significant correlation between the CBF and structural changes, including cortical volume, subcortical volume, surface area, and thickness in all participants, particularly AD patients after adjusting for age, sex, and APOE genotyping status.

Conclusion

Several structural abnormalities correlated with declined CBF and could potentially be used as imaging biological correlates biomarkers to predict early onset of AD, regardless of A β or tau accumulation.

1. Introduction

Alzheimer's disease (AD) is a type of neurodegenerative disease characterized by learning and memory impairment, personality changes, and executive dysfunction ¹. Although mental status examination and neuropsychological tests have been applied to assess the symptoms of mild cognitive impairment (MCI) and AD patients, neuroimaging methods such as magnetic resonance imaging (MRI) are used to identify structural changes in the AD brain ². However, these modalities are not adequate to diagnose AD because of the overlaps with brain changes in the normal aging. Neuroimaging findings have revealed that brain

atrophy and structural changes due to aging contribute strongly in the pathophysiology of AD and MCI ^{3, 4} and can support clinicians to diagnose AD ⁵. Neuroimaging studies have shown that the rate of whole-brain atrophy is a valuable marker to predict the progression of AD in patients with MCI ⁶. In addition, AD patients typically show atrophy in the medial temporal lobe ⁷, entorhinal cortex ⁸, and posterior cingulate cortex ⁹.

Benjamin et al., reported that structural changes are associated with hypometabolism in the large posterior neocortical regions of the brain in AD patients ¹⁰. Moreover, brain atrophy has been reported in the vast majority of neurological diseases. Previous studies indicated a significant correlation between the pattern of brain atrophy with Parkinson's disease ^{11, 12} and amyotrophic lateral sclerosis (ALS). Therefore, brain atrophy in MRI can be a reliable index to discriminate AD from other neurodegenerative diseases, particularly in the early onset of the disease. It has been well-documented that amyloid-beta (A β) and tau protein are involved in the pathophysiology of AD and responsible for neural degeneration and changes in the brain structure ¹³.

Cerebral small vessel disease, which is common in AD, has been reported as a pivotal cause of cognitive decline. White matter hyperintensities of presumed vascular origin (WMHs) can be observed on magnetic resonance imaging (MRI) using T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) sequences. Although WMHs are related to the brain atrophy and cognitive decline in AD, their mechanistic role is not understood ¹⁴. A decline in the regional cerebral blood flow (CBF) is proposed to be one of the initial changes in the AD process ¹⁵. However, the cause of this decline is not yet fully understood. Mattsson et al. reported an association between the A β and CBF pattern and proposed that declined CBF is an early consequence of neural death prior to considerable grey matter loss. It has been shown that brain atrophy in the AD patients is due to the accumulation of A β plaques, resulting in microvasculature disease and CBF impairment ¹⁶.

With regard to the role of amyloid plaques and neurofibrillary tangles in the AD brain pathology, investigating correlation between CBF and structural changes of the brain might reveal a different pathological pathway involved in the cortical and subcortical changes of the brain. Therefore, present study was undertaken to investigate the association between CBF with the structural changes in the cortical and subcortical regions of the brain in three groups of individuals, including normal control (NC), MCI, and AD subjects.

2. Materials And Methods

Participants and data acquisition

The participants' information was collected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://www.loni.usc.edu/>), launched by the Michael W. Weiner in 2003, as a public-private partnership. Primary endpoint of ADNI has been to examine whether serial MRI, positron emission tomography (PET), biological marker examinations, and clinical/neuropsychological assessments can be

combined to determine the progression of MCI and early AD. All participants with available data and imaging results were enrolled in this study. Demographic and clinical data of 149 subjects including 28 AD patients, 82 MCI patients, and 39 healthy subjects were obtained from the ADNI and analyzed in this study. The diagnostic status, Mini-Mental State Examination (MMSE) score, and the result of apolipoprotein E gene (APOE) genotyping for each subject were collected, as well.

MRI acquisition (T1, FLAIR)

All ADNI individuals had T1 structural MRI and T2-FLAIR acquired on a 1.5 Tesla (T) or 3T scanner from Siemens, Philips, or General Electric. The ADNIMRI protocol is described in detail by Jack et al.¹⁷. Accordingly, axial 3T FLAIR was acquired with voxel sizes of $0.85994 \times 0.8594 \times 5$ mm. Each image underwent quality control after acquisition at the Mayo Clinic (Rochester, MN), including image quality assessment, protocol compliance checks, and inspection for clinically significant medical abnormalities.

Automatic segmentation with Freesurfer V 7.0

Volumetric segmentation was performed using FreeSurfer image analysis suite, which is freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). The processing consisted of motion correction of multiple T1-weighted images, removal of non-brain tissues, automated Talairach transformation, segmentation of subcortical white matter and gray matter structures, automated topology correction, and intensity normalization.

Arterial spin labeling (ASL)-MRI processing

ASL-MRI, as a completely non-invasive procedure, was used to measure the CBF by exploiting the endogenous spins of arterial water as a proxy for blood flow. Also, labeling magnetization of arterial spins was inverted selectively. The Center for Imaging of Neurodegenerative Diseases (CIND) prepared perfusion-weighted images (PWI), computed a map of CBF, and conducted a regional analysis. ASL-MRI pre-processing consisted of three steps. The first step involved motion correction that ASL images were converted from DICOM to NiFTI format. In the second step, PWI computations were done and the ASL images were separated into the two groups of tagged and untagged, and the mean of each group was computed and saved. Next, the difference in the mean of the two groups was determined to obtain the PWI. The first untagged image was used as the reference for water density and termed "M0". M0 was used to calibrate the ASL signal for CBF computations and estimate the transformation from ASL-MRI and structural MRI, as an intermediate frame. The third step was intensity scaling of PWI, as well as the M0 image.

Statistical analysis

Before the statistical analysis, variables without a normal distribution were log-transformed to meet the normality assumption. Demographic variables were compared between the groups using the ANOVA test. Local associations between the CBF and structural variables were investigated using correlation models.

Partial correlation models were implemented for each association separately by adding CBF and structural variables (i.e., subcortical and cortical volume, thickness, and surface area) for each region and entering age, sex, and APOE-ε4 genotyping status as controlled variables. The bootstrapping method was used for addressing type I errors due to multiple comparisons. The significance level was set at 0.05, and statistical analysis was performed in SPSS version 22.

3. Results

Participants' characteristics

Table 1 presents demographic and clinical data of the participants. There was no significant difference in terms of age, education, and sex among the groups. However, AD patients had significantly lower MMSE scores and more APOE-ε4 carriers as compared to the MCI and CN groups.

Local correlation between CBF and subcortical volume

After implementing controlled correlation models, we found a significant local correlation between the CBF and subcortical volume in the groups (Table 2). In the AD group, only a local correlation was found in the fourth ventricle, whereas local correlations in the MCI group were observed in the third and fourth left and right lateral ventricles, as well as the right nucleus accumbens. Indeed, significant correlations were observed in the right pallidum, right vessel, and white matter of the left hemisphere cerebellum in the CN group.

Local correlation between CBF and thickness

In all AD patients, negative correlations were found in two regions, including posterior segment of the left middle frontal gyrus and the caudal part of the right anterior cingulate cortex (Table 3). The results of Pearson's correlation analysis showed a positive correlation between the CBF and thickness in several regions in the MCI group, including left entorhinal area, left and right lateral occipital cortices, left and right superior parietal lobules, right inferior parietal lobule, posterior part of the right middle frontal gyrus, right superior frontal gyrus, right inferior temporal gyrus, right pericalcarine, right postcentral gyrus, right precentral gyrus. In contrast, we found a negative correlation between right anterior cingulate cortex thickness and CBF. In healthy subjects, significant correlations were found between the left entorhinal area and the rostral part of the left anterior cingulate cortex with CBF.

Local correlation between CBF and cortical volume

Pearson correlation coefficient revealed a significant correlation between the CBF and cortical volume in the MCI and CN groups but not in the AD group (Table 4). In the MCI group, significant positive correlations were observed between CBF and following regions: left and right postcentral gyrus, left and right precentral gyrus, left and right precuneus, right precuneus, left and right posterior cingulate cortex, caudal and rostral parts of the left anterior cingulate, right superior frontal gyrus, left and right superior parietal lobules, right inferior parietal lobule, left and right superior temporal gyri, right transverse

temporal gyrus, left and right inferior temporal gyri, left middle temporal gyrus, left temporal gyrus, right lateral occipital gyrus, left and right supramarginal gyri, right insula, left entorhinal cortex, and right bankssts. In the CN group, significant positive correlations were found between CBF and left and right superior parietal gyri, right supramarginal gyrus, left entorhinal cortex, left fusiform gyrus, left medial orbital gyrus, anterior part of the left middle frontal gyrus, left temporal gyrus, right inferior temporal gyrus, and rostral part of the left anterior cingulate cortex.

Local correlation between CBF and surface area

Investigation of the local correlation between the CBF and surface area in the groups of study revealed that this correlation in the AD patients was meaningful in the left inferior temporal gyrus and isthmus of the left cingulate gyrus, as shown in Table 5. In the MCI group, this significance was more than other groups and was found in the left and right precuneus, right superior and inferior parietal lobules, right superior temporal gyrus, left and right transverse temporal gyri, left inferior and middle temporal gyri, left temporal pole, caudal and rostral parts of the left anterior cingulate gyrus, left posterior cingulate gyrus, left supramarginal gyrus, right middle orbital gyrus, right bankssts, and right fusiform gyrus. Moreover, significant correlations in the CN group were attributed to the following regions: right precentral gyrus, left and right superior parietal lobules, left and right supramarginal gyri, left fusiform gyrus, left and right lateral occipital gyri, right inferior and middle temporal gyri, and the orbital part of the left inferior frontal gyrus.

4. Discussion

In present study, our findings revealed a significant correlation between the CBF and structural changes, including cortical volume, subcortical volume, surface area, and thickness in all groups after adjusting for age, sex, and APOE genotyping status. To the best of our knowledge, this is the first study investigating the correlation between the CBF and structural changes, including cortical volume, subcortical volume, and surface area in patients with cognitive impairments.

Recently, Kim et al. revealed no significant association between the CBF and thickness in MCI patients and healthy people¹⁸. Generally, the CBF decline is one of the earliest events observed in patients with AD¹⁹. Evidence on CBF changes in patients with MCIs revealed that an increase or decrease in perfusion can be an early marker of neurodegeneration and may reflect metabolic demand changes in regions that are involved in cognitive function, including the temporal lobe, parietal lobe, frontal lobe, posterior cingulate gyrus, and precuneus^{20,21}. Neuroimaging studies have also found a decreased cortical cerebral blood flow (by 25 %) in patients with AD. Several mechanisms for this hypoperfusion have been proposed including constriction of brain arterioles, loss of vascular density and changes in neural activity patterns and/or in neurovascular coupling²². Also, alterations in cortical and subcortical regions, especially in the medial temporal lobe, have been observed, which are thought to be an indirect marker of neuronal damage in the preclinical phase of AD and can be detected by MRI^{23,24}. Moreover, cortical and

subcortical volume, surface area, and thickness may help diagnose AD and accurately predict the cognitive decline as a result of neurodegeneration ^{25, 26}.

Our findings revealed that changes in the CBF can predict structural changes in various brain regions, including the cortical and subcortical areas in AD, MCI, and healthy individuals. The correlations were mostly found in the medial temporal, temporal, parietal, occipital, and frontal regions, which are thought to be sensitive areas for the early pathology of AD ²⁷. More involved regions were detected in our study, including the precentral gyrus, pericalcarine cortex, entorhinal cortex, supramarginal gyrus, fusiform, pallidum, and ventricles. Notably, we found a correlation between the CBF and cortical volume and surface area in the posterior cingulate cortex and temporal pole of MCI patients, which are the main regions in the default mode network (DMN) ²⁸. It should be mentioned that this association was mostly observed in the preclinical stage of AD. Generally, the decline in CBF leads to the brain dysfunction, structural changes in the AD pathogenesis, and even death ²⁹.

According to our results, the CBF may be responsible for further structural changes and atrophy in the pathogenic course of AD; however, the mechanisms of this hypoperfusion in the early stages of neurodegeneration are unclear. Evidence shows that the CBF decline can lead to A β and hyperphosphorylated tau accumulation ³⁰. On the other hand, A β monomers have found to drive vasoconstriction in brain arterioles and potentially contributes to a reduction in resting cerebral blood flow and, therefore, CBF decline could be result of A β pathology ³¹. Recent studies suggest that A β can impair the fundamental mechanisms of blood supply regulation ^{32, 33}. However, several factors might account for this dysregulation in AD, such as impairment of endothelium-dependent responses, hypercontractile phenotype of cerebral smooth muscle cells, and vascular oxidative stress ³⁴. In this regard, Michels et al. observed a significant relationship between the CBF and APOE- ϵ 4, independent of A β accumulation in MCI and normal elderly individuals ³⁵. Moreover, other studies found CBF alterations in the right parahippocampal gyrus, bilateral cingulate gyri, and frontal regions in APOE- ϵ 4 carriers ³⁶.

We found strong correlations between the CBF and structural changes in the main brain regions involved in AD development, including the cingulate gyrus, temporal gyrus, and parietal lobule, which differ between healthy individuals and patients with AD and MCI ^{24, 35}. Although the role of tau pathology in neurodegeneration seems to be stronger than A β , both are associated with early pathological changes in AD ³⁷. According to our hypothesis, CBF may independently predict structural changes due to AD progression. However, it is still debatable whether the altered CBF is the cause or consequence of atrophy and structural changes ^{17, 38}.

In contrast to our findings, Luckhaus et al. found no significant association between atrophy and CBF in the early pathogenesis of AD ³⁷. Conversely, another study reported a significant correlation between CBF and cortical thickness in the prodementia stages ³⁹. Another study investigated the patterns of atrophy and hypoperfusion in MCI patients, compared to the controls, and found that both cerebral perfusion and

gray matter structure reduced in the entorhinal cortex and the isthmus cingulate cortex. However, in several regions, the CBF decline and atrophy were observed independently in MCI patients³⁹.

5. Conclusion

According to the present results, CBF decline, as measured by ASL-MRI, might predict future structural changes and causes neurodegeneration associated with AD development, regardless of A β or tau accumulation. However, there are some unresolved issues regarding the role of A β and tau pathologies in blood flow dysregulations and structural changes underlying the pathology of CBF impairment in the AD mechanisms; therefore, further research is needed in this area.

Declarations

Disclosure statement

No potential conflict of interest was reported by the author

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Tables

TABLE1. Participants characteristic

Demographic and health characteristic	CN(39)	MCI(82)	AD(28)	P value
Age, years	71.8(±6.8)	70.4(±7.4)	73.1 (±6.5)	0.186
Sex(M/F)	15/24	41/41	14/14	0.469
Education, years	16.2(±2.5)	16.5(2.7)	16.5(±2.2)	0.829
MMSE	28.9(±1.4)	28.3(±1.6)	23.9(±1.9)	0.000
APOE genotype				0.000
With out ε4	26	53	8	
One ε4	11	22	12	
Two ε4	1	7	8	

Values are showed as mean(±SD), Mini Mental State Examination(MMSE), results of One way ANOVA analysis between groups noted as p value

TABLE2. Significant Results of partial Correlation Analyses of CBF and subcortical volume within groups

Regions	Correlation coefficient	P value
AD		
4 th Ventricle	-0.529	0.007
MCI		
4 th Ventricle	-0.249	0.029
Left lateral ventricle	-0.346	0.002
Right lateral ventricle	-0.231	0.043
Right nucleus accumbens	0.244	0.030
3 th Ventricle	-0.263	0.021
CN		
White matter of left hemisphere cerebellum	0.596	0.000
Right pallidum	0.512	0.002
Right vessel	0.431	0.010

Cerebral blood flow (CBF), Alzheimer’s disease (AD), mild cognitive impairment (MCI), control normal (CN)

TABLE3. Significant Results of partial Correlation Analyses of CBF and Thickness within groups

Regions	Correlation coefficient	P value
AD		
Posterior part of left middle frontal	-0.457	0.033
Caudal part of right anterior cingulate	-0.544	0.005
MCI		
Left entorhinal area	0.237	0.035
Left lateral occipital	0.259	0.022
Right lateral occipital	0.284	0.012
Left superior parietal lobule	0.250	0.026
Right superior parietal	0.357	0.001
Posterior part of right middle frontal	0.288	0.010
Right inferior parietal lobule	0.316	0.005
Right inferior temporal	0.299	0.011
Right pericalcarine	0.234	0.039
Right postcentral	0.231	0.040
Right precentral	0.307	0.006
Rostral part of right anterior cingulate	-0.243	0.031
Right superior frontal	0.303	0.007
CN		
Left entorhinal area	0.400	0.017
Rostral part of left anterior cingulate	0.523	0.001

Cerebral blood flow (CBF), Alzheimer's disease (AD), mild cognitive impairment (MCI), control normal (CN)

TABLE4. Significant Results of partial Correlation Analyses of CBF and Cortical volume within groups

Regions	Correlation coefficient	P value
MCI		
Right postcentral	0.284	0.011
Right posterior cingulate	0.234	0.038
Right precentral	0.286	0.011
Right precuneus	0.387	0.000
Right superior frontal	0.248	0.027
Right superior parietal	0.372	0.001
Right superior temporal	0.257	0.029
Right supramarginal	0.266	0.018
Right transverse temporal	0.244	0.030
Right insula	0.255	0.023
Caudal part of left anterior cingulate	0.272	0.015
Left entorhinal	0.301	0.007
Left inferior temporal	0.244	0.039
left middle temporal	0.302	0.010
Left paracentral	0.264	0.019
Left postcentral	0.268	0.017
Left posterior cingulate	0.256	0.023
Left precentral	0.288	0.010
Left precuneus	0.360	0.001
Rostral part of left anterior cingulate	0.372	0.001
Left superior parietal	0.297	0.008
Left superior temporal	0.268	0.023
Left supramarginal	0.320	0.004
Left temporal	0.296	0.012
right bankssts	0.258	0.022
Right inferior parietal	0.460	0.000
Right inferior temporal	0.351	0.003
Right lateral occipital	0.274	0.015
CN		
Right superior parietal	0.348	0.041

Right supramarginal	0.346	0.042
Left entorhinal	0.383	0.023
Left fusiform	0.401	0.021
Left medial orbital	0.385	0.022
Anterior part of left middle frontal	0.374	0.027
Left superior parietal	0.412	0.014
Left temporal	0.368	0.035
Right inferior temporal	0.406	0.019
Rostral part of left anterior cingulate	0.523	0.001

Cerebral blood flow (CBF), Alzheimer's disease (AD), mild cognitive impairment (MCI), control normal (CN)

TABLE5. Significant Results of partial Correlation Analyses of CBF and Surface area within groups

Regions	Correlation coefficient	P value
AD		
Left inferior temporal	0.441	0.031
Isthmus of left cingulate	0.458	0.021
MCI		
Right precuneus	0.315	0.005
Right superior parietal	0.254	0.024
Right superior temporal	0.279	0.018
Right transverse temporal	0.243	0.031
Caudal part of left anterior cingulate	0.367	0.001
Left inferior temporal	0.238	0.044
left middle temporal	0.283	0.016
Left posterior cingulate	0.249	0.027
Left precuneus	0.312	0.005
Rostral part of left anterior cingulate	0.387	0.000
Left supramarginal	0.297	0.008
Left temporal pole	0.259	0.028
Left transverse temporal	0.252	0.025
Right bankssts	0.282	0.012
Right fusiform	0.274	0.020
Right inferior parietal	0.338	0.002
Right middle orbital	0.269	0.017
CN		
Right precentral	0.379	0.025
Right superior parietal	0.411	0.014
Right supramarginal	0.383	0.023
Left fusiform	0.458	0.007
Left lateral occipital	0.388	0.021
Orbital part of left inferior frontal	0.385	0.022
Left superior parietal	0.441	0.008
Left supramarginal	0.388	0.021
Right inferior temporal	0.415	0.016

Right lateral occipital	0.498	0.002
Right middle temporal	0.456	0.008

Cerebral blood flow (CBF), Alzheimer's disease (AD), mild cognitive impairment (MCI), control normal (CN)

Figures

Figure 1

Regions of interest are shown for significant correlation between structural values and regional cerebral blood flow. AD (green), MCI (blue), CN (red). Alzheimer's Disease (AD), mild cognitive impairment (MCI), control (CN)