Regional cerebral blood flow decline can predict atrophy in Alzheimer's disease spectrum

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease characterized by symptoms such as dementia, personality changes, and executive dysfunction. Brain atrophy and structural changes based on the MRI play an important role as a valid biomarker of AD and can support the clinical diagnosis of AD. The decline in the regional cerebral blood flow (rCBF) is believed to be among the first changes in Alzheimer's continuum. The reason for this reduction in cerebral blood flow is not fully understood yet. Previous studies revealed the association between amyloid-beta and rCBF pattern and suggested that reduced rCBF is an early consequence of neural death and is prior to the considerable grey matter loss. In this study we investigated the association between rCBF and brain structural changes in three different groups of subjects consisted of control (CN), MCI, and AD groups. Our findings revealed a significant correlation between rCBF and structural changes including cortical volume, subcortical volume, surface area, and thickness in all groups after adjusting for age, sex, and APOE genotyping status. As our investigation, cerebral blood flow as measured by ASL-MRI might independent from Aβ and tau accumulation predict future structural changes and causes neurodegeneration in relation to AD development.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by symptoms such as dementia, personality changes, and executive dysfunction (1). physicians may use mental status testing and neurophysiological tests to assess symptoms of the patients. Imaging methods like computed tomography (CT) , and magnetic resonance imaging (MRI) were used to rule out other probable causes of dementia (2). However, these scans are not enough to diagnose AD because of the overlap with the normal aging changes in the brain.

Brain atrophy and structural changes based on the MRI play an important role as a valid biomarker of AD (3, 4) and can support clinical diagnosis of AD (5). Based on the previous studies it can be concluded that rates of the atrophy of the whole brain can be excellent biomarkers to predict progression of the disease in the subjects with mental cognitive impairment (MCI) (6). AD patients typically show levels of atrophy in the medial temporal lobe (7), entorhinal cortex (8), and the posterior cingulate region (9).According to the findings of Benjanin et al structural changes are associated with hypometabolism in the large posterior neocortical regions of the brain in AD patients (10).

Decline in the regional cerebral blood flow (rCBF) is believed to be among the first changes in Alzheimer's continuum (11). The reason of this reduction in the cerebral blood flow is not fully understood yet. N. Mattsson et al revealed the association between amyloid beta and rCBF pattern and suggested that reduced rCBF is an early consequence of neural death and is prior to the considerable grey matter loss

(12). In this study we investigated the association between rCBF and brain structural changes in three different groups of subjects consisted of control (CN), MCI, and AD groups.

Atrophy in the brain is has been seen in a vast majority of neurological diseases. There is a significant correlation between patterns of atrophy and Parkinson's disease (13, 14) and patients with amyotrophic lateral sclerosis (ALS) (17).Thus, we hypothesize that existence of the reduced levels of cerebral blood flow alongside atrophy in MRI could be a reliable biomarker to discriminate AD from other neurodegenerative diseases at the early onset of the disease.

It has been said repeatedly that amyloid beta (Aβ) and tau protein, which are the principal molecular changes in the AD pathology ,are in charge of the changes in the brain structure (15). According to the findings of the several studies atrophy in the brain of the AD patients is due to the accumulation of the amyloid beta (Aβ) plaques (12). Beside the impact of amyloid plaques and neurofibrillary tangles on the brain, Our investigation in the correlation between rCBF and structural changes of the brain might suggest a different pathological pathway that leades to the brain cortical and subcortical changes. Further investigations would reveal the probable role of reduced rCBF in structural changes in the cortical and subcortical regions of the brain.

Materials And Methods

Data Acquisition

Participants' information was acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI led by Principal Investigator Michael W. Weiner, MD was launched in 2003 as a public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). We enrolled 149 subjects including 28 patients AD diagnosed, 82 MCI patients, and 39 healthy subjects from ADNI. Diagnostic status, MMSE scores and results of APOE genotyping for each subject available at ADNI. All subjects with available required imaging variables were added.

MRI processing

In this study volumetric segmentation is done with the freesurfer available for download online (http://surfer.nmr.mgh.harvard.edu/). The processing consisted of motion correction of multiple T1 weighted images, removing non-brain tissue, automated Talairach transformation, segmentation of subcortical white matter gray matter structures, automated topology correction, and intensity normalization. ADNIGO and ADNI2 are being run with version 5.1 of freesurfer. In ADNIGO an accelerated

and a non-accelerated T1 image are acquired for each subject. Both images are pre-processed by Mayo Clinic. Processing is consisted of three steps. Autorecon-1 command initiates multiple tasks such as: motion correction, non-uniform intensity normalization (NU), Talairach transform computation, and intensity normalization 1 skull strip. Autorecon -2 command creates white matter and pial surfaces and is involved in segmentation of grey and white matter structures. The autorecon-3 creates the cortical parcellation.

ASL-MRI processing

In this study Arterial Spine Label (ASL) was used to measure cerebral blood flow which is completely noninvasive and is performed by exploiting the endogenous spins of arterial water as a proxy for blood flow. For labeling magnetization of the arterial spins is inverted selectively. The center for imaging of neurodegenerative diseases (CIND) prepares perfusion weighted images (PWI) and computes a map of CBF and a regional analysis. The ASL-MRI pre-processing is consisted of three steps. First step is motion correction in which the ASL images are converted from DICOM to NiFTI format. In the next step PWI computations take place. The ASL images are separated into two groups of tagged and untagged images and the mean of each group is computed and saved. Then in order to obtain a PWI the difference of the mean of two groups in taken. The first untagged image is used to reference the water density and termed M0. The M0 is used to calibrate the ASL signal for the CBF computations and to estimate the transformation from the ASL MRI and structural MRI as an intermediate frame. The third step is intensity scaling of the PWI as well as the M0 image. The detailed procedure is available on (adni.loni.usc.edu).

Statistical analysis

Prior to statistical analysis, non normal distributed variables were log transformed to meet normality assumption. demographical variables were compared between groups using ANOVA. Local association between rCBF and structural variables investigated using correlation models. We implemented partial correlation models for each association separetly by adding rCBF and structural variables (subcortical and cortical volume, thickness, and surface area) for each region and entering age, sex, and APOE ε4 genotyping status as controlled variables. We used bootstrapping method for addressing type I error due to multiple comparison. Significance levels >0.05 was applied. The statistical analysis were done using SPSS16.

Results

Participants characteristics

Table1 shows the demographical data of participants. There was no difference in age, education and sex between groups. AD group has significant lower MMSE score as expected and AD group has more APOE ε4 carriers than other groups.

Local correlation between rCBF and subcortical volume

After implementing controlled correlation we found a significant local correlation between rCBF and subcortical volume in groups. In AD group we only find correlation in 4^{th} ventricle, however in MCI the significant regions observed in 3th, 4^{th}, left and right lateral ventricles, and Right nucleus accumbens (Tab2). Also there is correlation in Right pallidum, Right vessel, and White matter of left hemisphere cerebellum in CN group (Tab2).

Local correlation between rCBF and thickness

Across all AD patients we only find negative correlation in two regions including posterior part of left middle frontal and caudal part of right anterior cingulate (Tab3). Pearson's correlation showed a correlation between rCBF and thickness in widespread regions among MCI group (Tab3). This significant relation was observed in left entorhinal area, left and right lateral occipital, Left and right superior parietal lobule, Right inferior parietal lobule, Posterior part of right middle frontal, Right superior frontal, Right inferior temporal, Right pericalcarine, Right postcentral, Right precentral, and Rostral part of right anterior cingulate (Tab3). In healthy participants the correlation exist in Left entorhinal area and Rostral part of left anterior cingulate (Tab3).

Local correlation between rCBF and cortical volume

Results demonstrate the significant correlation between rCBF and cortical volume only in MCI and CN groups (Tab4). We found a wide positive correlation in left and right postcentral, left and right precentral, left and right precuneus, right precuneus, left and right posterior cingulate, caudal and rostral part of left anterior cingulate , right superior frontal, left and right superior parietal, right inferior parietal, left and right superior temporal, right transverse temporal, left and right inferior temporal, left middle temporal, left temporal, right lateral occipital, left and right supramarginal, right insula, left entorhinal, and right bankssts in MCI patients (Tab4). Significant results was fewer in CN group which involve left and right superior parietal, right supramarginal, left entorhinal, left fusiform, left medial orbital, anterior part of left middle frontal, left temporal, right inferior temporal, and rostral part of left anterior cingulate (Tab4). There is no considerable correlation in AD individuals.

Local correlation between rCBF and surface area

Investigating the local association between rCBF and surface area in our groups revealed that in AD patients, this correlation observed in left inferior temporal and isthmus of left cingulate (Tab5). As results described in Table5, significant correlations in MCI group similar to previous models was more than other

groups (Tab5). rCBF and surface area was correlate in left and right precuneus, right superior and inferior parietal, right superior temporal, left and right transverse temporal, left inferior and middle temporal, left temporal pole, caudal and rostral part of left anterior cingulate, left posterior cingulate, left supramarginal, right middle orbital, right bankssts, and right fusiform in MCI patients (Tab5). Also in CN group, significant correlations observed in regions including right precentral, left and right superior parietal, left and right supramarginal, left fusiform, left and right lateral occipital, right inferior and middle temporal, and orbital part of left inferior frontal (Tab5).

Discussion

Our findings revealed a significant correlation between rCBF and structural changes including cortical volume, subcortical volume, surface area, and thickness in all groups after adjusting for age, sex, and APOE genotyping status. as our knowledge this is the first study investigate the correlation between regional cerebral blood flow with structural changes including cortical volume, subcortical volume and surface area in patients with cognitive impairments. Recently Kim et al. study revealed no association between rCBF and thickness in MCI patients and healthy peoples (16).

Cerebral blood flow decline is one of the earliest events that arise in patients with AD (17). The evidence investigated CBF changes in those with MCI revealed, increase or decrease in perfusion can be an early marker of neurodegeneration and may reflect metabolic demands changing in regions that involve in cognitive function including temporal, parietal, frontal, posterior cingulate, and precuneus (18, 19). Also alterations in cortical and subcortical regions importantly in medial temporal lobe that are thought to be an indirect reflection of neuronal damage in preclinical phase of AD and which can be detect by magnetic resonance imaging (MRI) (20, 21). Moreover, cortical and subcortical volume, surface area, and thickness may help diagnose AD and accurately predict cognitive decline in result of neurodegeneration (22, 23).

Our findings revealed changes in rCBF can predict structural changes in widespread regions including cortical and subcortical areas in AD, MCI and healthy subjects. The correlation mostly found in medial temporal, temporal, parietal, occipital and frontal which thought to be sensitive regions for early pathology of AD (24). Our significant regions was even wider and observed in precentral, pericalcarine, entorhinal area, supramarginal, fusiform, pallidum, and ventricles. Notably we found a correlation between rCBF and cortical volume or surface area in posterior cingulate cortex and temporal pole in MCI patients which are signature regions of default mode network (DMN) (25). It should be mentioned that this association were mostly observed in preclinical stage of AD compared to other groups according to our results.

The decline of cerebral blood flow (CBF) leads to brain dysfunction, death, and consequently structural changes in AD pathogenesis (26). As our results rCBF may be responsible for further structural changes and atrophy in pathogenic course of AD, however, the mechanism of hypoperfusion in early stages of neurodegeneration is unclear. Evidence indicate the rCBF decline can lead to Amyloid β and hyperphosphorylated tau accumulation (26), despite this some evidence revealed rCBF can be result of

Aβ pathology (27). Studies suggest that Aβ can impairs the fundamental mechanisms of blood supply regulation (28, 29). On the other hand several factors might be account for dysregulation in AD includes impair of endothelial-dependent responses, hypercontractile phenotype of Cerebral smooth muscle cells, and Vascular oxidative stress (30). Michels et al. observed the significant relation between rCBF and APOE ε4 independent of Aβ in MCI and normal elderly (31). Moreover, other studies found a rCBF alteration in right parahippocampal gyrus, bilateral cin-gulate gyri, and frontal regions in APOE ε4 carriers (18, 32).

We found the strong correlation between rCBF and structural changes in signature regions involve in AD development including cingulate gyrus, temporal gyrus, and parietal lobule which in recent studies differs in AD and MCI compare to healthy subjects (33, 34). Role of tau pathology in neurodegeneration seems to be more stronger than Aβ, however both are associated with early pathological changes in AD (35). As our hypothesis cerebral blood flow might independently predict structural changes due to AD progress. However, itis still debatable whether alterated CBF is the cause or consequence of atrophy and structural changes (16). In contrast to our findings Luckhaus et al. found no association between atrophy and CBF in early pathogenesis of AD (36). Having said that another study observed a correlation between CBF and cortical thickness in predementia stages (37). Another research investigated the pattern of atrophy and hypoperfusion in MCI compare to CN, found that both cerebral perfusion and gray matter structure reduced in entorhinal and isthmus cingulate, in spite of this in several regions, CBF decline and atrophy in absence of each other were observed in MCI (38).

Conclusion

As our investigation cerebral blood flow as measured by ASL-MRI might independent from Aβ and tau accumulation predict future structural changes and causes neurodegeneration in relation to AD development. However there is some unsolved issues for example the role of Amyloid and tau pathology in blood flow dysregulation and structural changes underlying pathology and the significance of CBF in the AD mechanism and more research is needed.

Declarations

Data used in this article's preparation were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at:

http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

The declaration of interest:

None. The authors declare no competing interests.

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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		
4th Ventricle	-0.529	0.007
MCI		
4th 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
3th 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)