Ratio of $\text{A}\beta_{42}/\text{P-tau}_{181p}$ in CSF is associated with aberrant default mode network in AD

Xiaozhen Li$^1$, Tie-Qiang Li$^2$, Niels Andreasen$^3$, Maria Kristoffersen Wiberg$^4$, Eric Westman$^1$ & Lars-Olof Wahlund$^1$

$^1$Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden, $^2$Department of Medical Physics, Karolinska Huddinge, Karolinska Institutet, Stockholm, Sweden, $^3$Alzheimer Disease Research Center, Karolinska Institutet, Stockholm, Sweden, $^4$Department of Clinical Science, Intervention, and Technology, Karolinska Institute, Stockholm, Sweden.

The default mode network (DMN) is particularly relevant to Alzheimer’s disease (AD) since its structures are vulnerable to deposition of amyloid. Decreased levels of $\beta$-amyloid$_{1-42}$ ($\text{A}\beta_{42}$) and increased total tau protein (T-tau) and tau phosphorylated at position threonine 181 (P-tau$_{181p}$) in cerebrospinal fluid (CSF) have been established as valid biomarkers for the diagnosis and prognosis of AD. However, the relationship between CSF biomarkers and change in the DMN is still unknown. In this study we investigated the correlation between the functional connectivity within the DMN and the ratio of $\text{A}\beta_{42}/\text{P-tau}_{181p}$ in the CSF. We found that the ratio of $\text{A}\beta_{42}/\text{P-tau}_{181p}$ was moderately positively correlated with the functional connectivity within the DMN in the left precuneus/cuneus. This finding implicates that the brain functional connectivity within DMN is affected by pathological changes at early stage in AD. This may provide a better understanding of AD pathology progression and improve AD diagnosis.

Alzheimer’s disease (AD) is the most common dementia in elderly people. The pathological hallmarks of AD are amyloid plaques (AP) and neurofibrillary tangles (NFT). These proteins are made up of $\beta$-amyloid$_{1-42}$ ($\text{A}\beta_{42}$) and tau phosphorylated at position threonine 181 (P-tau$_{181p}$), respectively$^1$. Such brain changes occur decades before the onset of dementia, leading to progressive loss of functions, metabolic alterations and structural changes in the brain$^2$. Immunocytochemical and biochemical analyses in AD biopsies and autopsies indicated that synaptic loss in the hippocampus and neocortex is another early event and currently the best neurobiological correlate of cognitive deficits in AD. There are growing evidences that still living neurons lose their synapses in AD and soluble assembly states of $\text{A}\beta$ peptides can cause cognitive problems by disrupting synaptic function in the absence of significant neurodegeneration$^1$.

The brain is in direct contact with the cerebrospinal fluid (CSF). Biochemical changes that reflect pathophysiologic processes in the brain are reflected in the CSF$^4,5$. Both $\text{A}\beta_{42}$ and tau proteins of CSF can be reliably measured$^7$. The clinical and diagnostic usefulness and validity of these CSF biomarkers in AD patients have been supported by numerous studies$^8$. In comparison with healthy elderly and patients with other dementia, AD patients have been found to have decreased levels of $\text{A}\beta_{42}$ and increased levels of total tau protein (T-tau) and P-tau$_{181p}$ levels in CSF$^{9,10}$. Mild cognitive impairment (MCI) is recognized as the prodromal stage of AD, representing a transitional period between normal aging and AD$^{11}$. More than half of the MCI patients progress to dementia within 3 to 5 years$^{12}$. There is evidence indicating that subjective cognitive impairment (SCI), also referred to as subjective memory complaints, is a stage prior to MCI in the eventual development of AD dementia$^{14}$. A CSF AD profile is also common in patients with MCI and SCI. Levels of $\text{A}\beta_{42}$, T-tau and P-tau$_{181p}$ in the CSF are strongly associated with future development of AD, which has been proven in many studies$^{15,16}$.

During the past years, changes in resting-state functional MRI (rs-fMRI) have been used to study the pathophysiology of AD and MCI. As a biomarker of synaptic dysfunction, rs-fMRI may demonstrate abnormality very early in AD$^{17}$. The rs-fMRI studies for AD have primarily focused on a characteristic set of brain regions, including the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC)/precuneus and parietal cortex. Some studies have also investigated the sub-regions of the medial temporal lobe (MTL) including hippocampus (HC), parahippocampal gyrus (PHG) and middle temporal gyrus (MTG). This collection of brain regions that are deactivated during a broad range of cognitive tasks and believed to support a default mode activity of the human brain has been defined as the default mode network (DMN)$^{18}$. 
Altered connectivity within the DMN in AD and MCI has also been reported in many studies. As expected, AD subjects had the lowest mean MMSE score, concentration of CSF Aβ42 and ratio of Aβ42/P-tau181p, while the T-tau and P-tau181p were the highest among the four groups.

Voxel-wise correlation analysis result showed one statistical significance cluster with positive correlation between the ratio of Aβ42/P-tau181p and functional connectivity within the DMN, adjusted for age, gender and grey matter intensity map (Figure 1). The cluster consist of 17 voxels, peak T score is 3.44 and located in left precuneus. However, the most part of cluster is in the left cuneus.

Results

Ninety-seven subjects were included for the final data analyses including: 21 AD, 36 MCI, 23 SCI and 17 other dementias (OD) patients. The conventional MRI for all subjects showed no abnormality other than brain atrophy and age related white matter changes. The demographics and clinical data are shown in Table 1. As expected, AD subjects had the lowest mean MMSE score, concentration of CSF Aβ42 and ratio of Aβ42/P-tau181p, while the T-tau and P-tau181p were the highest among the four groups.

Voxel-wise correlation analysis result showed one statistical significance cluster with positive correlation between the ratio of Aβ42/P-tau181p and functional connectivity within the DMN. To test the hypothesis, we measured the ratio of Aβ42/P-tau181p and the functional connectivity in DMN.

Table 1 | Demographics of subjects

|       | AD       | MCI      | OD        | SCI       |
|-------|----------|----------|-----------|-----------|
| Number| 21       | 36       | 17        | 23        |
| Age   | 65.6 ± 7.1 | 60.4 ± 9.2 | 59.3 ± 8.1 | 57.6 ± 9.1 |
| Gender (M/F) | 8/13     | 17/19    | 12/5      | 9/14      |
| MMSE  | 22.3 ± 5.2 | 26.1 ± 3.2 | 23.0 ± 4.0 | 27.7 ± 2.4 |
| Aβ42 (pg/mL) | 483.8 ± 130.8 | 841.7 ± 352.1 | 935.4 ± 258.8 | 1101.0 ± 304.3 |
| T-tau (pg/mL)  | 634.7 ± 275.9 | 356.8 ± 197.8 | 248.5 ± 103.3 | 276.7 ± 122.4 |
| P-tau181p (pg/mL) | 88.9 ± 32.9 | 58.8 ± 24.2 | 43.8 ± 14.2 | 51.8 ± 19.4 |
| Aβ42/P-tau181p | 6.6 ± 4.5 | 18.0 ± 11.0 | 24.2 ± 10.4 | 22.9 ± 6.4 |
| GM    | 406.6 ± 45.1 | 430.1 ± 38.1 | 423.9 ± 41.4 | 450.9 ± 35.4 |
| ICV   | 1087.6 ± 48.1 | 1092.5 ± 98.4 | 1112.5 ± 78.3 | 1115.5 ± 95.8 |

Data are represented as mean ± standard deviation. Key: AD, Alzheimer’s Disease; MCI, Mild Cognitive Impairment; OD, non-AD dementia; SCI, Subjective Cognitive Impairment; M, Male; F, Female.

CSF biomarkers reference: Aβ42 < 450 pg/mL, T-tau > 400 pg/mL, P-tau181p > 80 pg/mL.

Discussion

To our knowledge, this study is the first one to investigate the relationship between CSF biomarkers and functional connectivity change within the DMN in AD. The main finding of this study is that the CSF ratio of Aβ42/P-tau181p is moderately positively corre-
lated with the functional connectivity within the DMN in the left precuneus/cuneus.

Concentrations of Aβ42, T-tau and P-tau181p in CSF may be sensitive biomarkers of incipient NFT and AP formation in AD. Seppälä et al. demonstrated that amyloid plaques and hyperphosphorylated tau in cortical brain biopsies reflected low CSF Aβ42 and high CSF T-tau/P-tau181p levels, respectively. It has been reported that CSF Aβ42 concentrations are decreased, while T-tau and P-tau181p concentrations are increased in AD, even in MCI and SCI patients. In line with this, we found 13 MCI and 3 SCI subjects with decreased CSF Aβ42 and/or increased T-tau and P-tau181p. Herukka et al. reported that the combination of Aβ42 and P-tau181p was the most predictive assay for AD among MCI patients and this maybe a sensitive marker of AD pathology. To build on this, we used the CSF ratio of Aβ42/P-tau181p as a pathology marker to investigate the relationship between AD pathology and functional connectivity changes.

Interestingly, the majority of regions with amyloid deposition in AD patients, assessed with positron emission tomography (PET), overlap with the DMN. In AD and MCI patients, decreased functional connectivity within the DMN have been reported, and progressed with disease severity. Furthermore, the functional connectivity between brain regions of the DMN is disrupted in elderly normal adults with amyloid deposition. There is evidence that soluble oligomers of Aβ can selectively impair synaptic plasticity to disrupt synaptic function both in mice model and in vitro. In this study, a positive correlation in precuneus/cuneus between the CSF ratio of Aβ42/P-tau181p and Z-score of left precuneus/cuneus in AD patients is decreased in AD patients and in cognitively impaired subjects with AD-like pathological changes. Further, increased Aβ burden in precuneus/cuneus was associated with increased brain atrophy rate in MCI patients. Although cuneus have not received considerable attention in previous reports, cuneus might offer an important structural support to the DMN.

ICA provided a measure of the magnitude of the DMN co-activation. In this study, the Z-score change of the left precuneus/cuneus is similar to the trend of CSF ratio of Aβ42/P-tau181p with AD progression. The Z-score is correlated with CSF Aβ42/P-tau181p for all AD, MCI and SCI subjects. There was only a moderate significant correlation in the MCI group when calculating the correlation for individual diagnostic groups. These results indicate that both the CSF Aβ42/P-tau181p and the DMN activity changes in AD are parallel to each other only at some stage. In Sperling’s hypothetical model of

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**Table 2 | Partial correlation test results between Z-score of left precuneus/cuneus and CSF ratio of Aβ42/P-tau181p for AD, MCI and SCI subjects, controlled by age and gender**

|        | Aβ42/P-tau181p | Z-score | r     | p     |
|--------|----------------|---------|-------|-------|
| Total  | 16.4 ± 10.5    | 1.93 ± 1.01 | 0.325 | 0.003 |
| AD     | 6.6 ± 4.5      | 1.64 ± 1.03 | 0.033 | 0.895 |
| MCI    | 18.0 ± 11.0    | 1.98 ± 0.99 | 0.499 | 0.003 |
| SCI    | 22.9 ± 6.4     | 2.13 ± 0.99 | −0.084 | 0.718 |

Data are represented as mean ± standard deviation. Key: r, Pearson correlation coefficient; AD, Alzheimer’s Disease; MCI, Mild Cognitive Impairment; SCI, Subjective Cognitive Impairment.

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Figure 2 | Scatter plots graph of partial correlation analysis result for AD, MCI and SCI subjects in total. There is a moderate correlation (r = 0.325, p = 0.003) between ratio of Aβ42/P-tau181p and Z-score of left precuneus/cuneus (adjusting for age and gender).

Figure 3 | Scatter plots graphs of partial correlation analysis result for AD, MCI and SCI subjects separately. Scatterplots graphs show partial correlation between ratio of Aβ42/P-tau181p and Z-score of left precuneus/cuneus in (a) AD, (b) MCI and (c) SCI respectively (adjusting for age and gender). There is a moderate significant positive correlation in the MCI group (b) and r is 0.499 (p = 0.003).
dynamic biomarkers, rates of change in each biomarker vary over time, representing a sigmoid shaped time course. At a given point, the slopes (rate of change) of biomarkers might be different although they have the same shape over the course of disease progression. This is in line with what our results shows, a relationship between CSF and synaptic dysfunction biomarkers. The rate of change in Aβ42/P-tau181p is similar to the DMN activity change in the MCI stage, but different rates in AD and SCI stages. This temporal lag may be altered by factors such as brain reserve, cognitive reserve and the added contributions of coexisting pathologies17. This study has several limitations. First, the sample size is limited. Second, some selected variables were controlled, but there might still be factors confounding the association such as APOE gene. Third, the correlations between the CSF ratio of Aβ42/P-tau181p and functional connectivity in the DMN was assessed at only one time point, additional longitudinal work is warranted. Fourth, the presence of occult AD-related neurodegenerative processes based on the presence of altered CSF Aβ42 and P-tau181p concentrations without autopsy confirmation of NFTs and APs was inferred.

In summary, the results implicate a connection between biochemical AD pathology and functional connectivity within the DMN. Although the correlation is weak between functional connectivity and the CSF ratio of Aβ42/P-tau181p, aberrant DMN may reflect pathology changes in AD. This investigation is beneficial to further understanding of the relationship of CSF Aβ42, P-tau181p, and synaptic dysfunction at different stages of AD. Moreover, it may help us to better understand the AD pathology progression and diagnose AD at an early stage.

**Methods**

Participants. A total of 110 subjects (97 included in the present study, 13 excluded due to image quality issues) were consecutively recruited from the Memory Clinic at the University Hospital of Karolinska Huddinge, in Stockholm, Sweden, from November 2010 to February 2012. The study was approved by Regional ethics committee in Stockholm (Dnr 2011/86-31/4) for human studies prior to the start of the data collection. All participants underwent a clinical examination in a comprehensive manner, including physical and psychiatric evaluations, MRI scans, lumbar puncture and blood analyses, as well as neuropsychiatric, linguistic and occupational therapeutic examinations. Informed consent was obtained from all subjects. For those patients who were unable to give informed consent, informed consent was obtained from their legal guardian.

Clinical diagnoses were made according to established international criteria. AD and OD were diagnosed according to DSMIV/ICD-10 criteria. MCI was defined using Winblad et al. criteria46. Patients categorized as SCI had cognitive complaints at an early stage.

MRI imaging. All MRI image data sets were acquired on a Siemens whole-body clinical MRI 3T scanner (Magnetom Trio, Erlangen, Germany) equipped with 32-channel phase-array head coil. The MRI protocol included a high-resolution sagittal 3D T1-weighted image acquired with MPAGE sequence, TR/TE = 1900/2.57 ms, 176 sagittal slices, voxel size 1 × 1 × 1 mm, and flip angle = 9°. The rs-fMRI measurements lasted 10 min and 30 s. The main acquisition parameters included: TR/TE = 1600/35 ms, 400 time frames of gradient recalled echo EPI, and 42 contiguous oblique slices of 4 mm thick, FOV = 240 mm, matrix = 64 × 64, parallel data acquisition with an acceleration factor of 2. The slices were all parallel to the plane of the anterior and posterior commissure line. During the acquisition of the rest-state fMRI, the subject was instructed to close their eyes, not to think anything in particular and not to fall asleep.

**Data analysis.** Structural MRI data analysis was performed using a VBM protocol with FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/). The images were segmented into grey matter, white matter and CSF, and co-registered to the MNI template.

All rs-fMRI data were carried out using AFNI (http://afni.nimh.nih.gov/afni). The following pre-statistics processing was applied: exclusion of the first 10 time frames in each data set to ensure that the rs-fMRI signal reached the steady state; correction for slice-dependent time shifts; head motion correction by using 3dvolreg based on 6-parameter rigid body image registration (subjects who had more than 3 mm movement were excluded from further analysis); spatial smoothing with a Gaussian kernel of 4-mm full width at half maximum (FWHM); and transformed to MNI152 standard space to yield a volumetric time series resampled at 4 mm isotropic voxels. A temporal band-pass filter was performed within the frequency range of 0.01–0.1 Hz. After pre-processing, data were entered into a spatial independent component analysis (ICA) using the Group ICA of fMRI Toolbox (GIFT) version 1.3i (http://mialab.mrn.org/software/gift), which was implemented in MATLAB (MathWorks, Massachusetts, U.S.A) and established for the analysis of fMRI data. Afterward, 20 meaningful components were extracted after the ICA group analysis. For comparison, individual data set was scaled to Z-score to compensate for inter-individual differences in measured signal levels as previous study.82 DMN component was selected by visual inspection based on the anatomy reported previously.82 The individual DMN component map was entered into one-sample t-test using 3dttst+ program in AFNI to determine correlation with the ratio of Aβ42/P-tau181p controlled by age, gender and grey matter intensity map. Grey matter intensity map is a voxel-level covariate. A threshold at t > 2.9 and a minimum spatially connected cluster size > 110 voxels were employed. The Monte Carlo inference using the AlphaSim program from AFNI indicated that the statistical significance is at least p < 0.05 when the uncorrected voxel threshold was set at 0.005. Region of interest (ROI) masks were created using cluster with statistical significance. The average t-scores of ROIs were calculated using 3dmaskave program in AFNI. Controlled by age and gender, the partial correlation between CSF ratio of Aβ42/P-tau181p and ROI Z-score was tested both for AD, MCI, SCI subjects in total and separately, which were performed with SPSS software package version 20.0 (SPSS, Chicago, IL., U.S.A.).

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Author contributions

T.-Q.L. and L.-O.W. designed the study and oversight the execution of the research program. N.A. and L.-O.W. recruited and clinically evaluated the subjects. M.K.W. was responsible for the execution of the MRI data acquisition protocol. X.L. is the dedicated Ph.D. student for the project and was mainly responsible for the data collection and analysis. X.L. prepared also the manuscript with supervisions from E.W., T.-Q.L. and L.-O.W.

Additional information

Competing financial interests: The authors declare no competing financial interests.

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