Altered hippocampal functional connectivity in patients with mild cognitive impairment who are at risk of developing Alzheimer's disease – evidence from resting state fMRI and cerebrospinal fluid biomarkers

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Introduction: Alzheimers´ disease (AD) affects the integration and coordination of neuronal activity between cortical brain regions. Diagnostic markers for incipient AD are of great interest to enable prevention and early treatment to prevent further progress of the disease. Earlier studies have shown a strong association between certain CSF biomarkers and future development of AD in patients with mild cognitive impairment (MCI) [1]. Specifically, the combination of total tau (T-tau), amyloid β_{1-42} (Aβ42) and phosphorylated tau at threonine 181 (P-Tau_{181}) yielded a sensitivity of 95% and a specificity of 87% for detection of incipient AD in patients diagnosed with MCI. Another line of investigation regarding AD, is the study of resting state networks, more specifically the default mode network (DMN) [2,3]. In this work, we evaluated whether the combination of CSF biomarkers and changes in functional connectivity within the DMN, assessed using resting state fMRI, can differentiate between patients with and without pathological CSF biomarkers.

Subjects and methods: Resting state fMRI was performed on patients diagnosed with mild cognitive impairment (MCI). Two sub groups were included: 1) MCI with pathological CSF (Aβ42/ P-Tau_{181} ratio < 6.5 [1], 5 males, 6 females, mean age 71.8), and 2) MCI with non-pathological CSF (7 males, 9 females, mean age 72.2). Imaging was performed on a Siemens Magnetom Trio 3T system (Erlangen, Germany). Resting state measurements were acquired using a Gradient-Echo EPI pulse sequence (TR/TE=2000/30 ms, voxel size 3×3×3 mm^3, 33 slices). Subjects were instructed to close their eyes, and remain awake during the experiment. Anatomical images were acquired using a 3D T1-MPRAGE pulse sequence (TR/TE = 1950/3.4 ms, voxel size 1×1×1.2 mm^3, 178 slices). Preprocessing of the functional data was performed using SPM8 [http://www.fil.ion.ucl.ac.uk/spm] and included slice time correction, motion correction, normalization into standard MNI space and spatial smoothing (FWHM = 6 mm). Signal from CSF and white matter were regressed out of the data. Also, motion parameters were entered as covariates of no interest. Prior to functional connectivity assessment, all data were band-pass filtered, retaining frequencies in the range 0.01 – 0.1 Hz. Functional connectivity was assessed using Pearson's correlation ratio between time courses obtained by averaging all voxels within each of 10 volumes of interest (VOI), corresponding to nodes of the DMN (Table 1). The 10 VOIs (normalized into MNI space) were created using the WFU_PickAtlas toolbox [4]. Mean VOI-to-VOI connectivity values for each group (Fisher-transformed correlation coefficients) were compared using Student's T-test. Furthermore, principal component analysis (PCA) was applied to the full VOI-to-VOI connectivity data for all subjects. PCA dimensionality reduction was, thus, performed on the result matrix having 27 rows (11+16 subjects) and 45 columns (unique correlation values per subject). The first two principal components were visualized, and a linear discriminant analysis was performed, for which sensitivity and specificity was calculated (Fig.1).

Table 1: Volumes of interest and sizes used for time course correlation analyses

Default mode network region	Size (voxels)
Anterior cingulate cortex (ACC)	3110
Left hippocampus (HIPP_L)	1296
Right hippocampus (HIPP_R)	1318
Left lateral parietal cortex (LPC_L)	5440
Right lateral parietal cortex (LPC_R)	4385
Left medial temporal cortex (MTC_L)	5951
Right medial temporal cortex (MTC_R)	5361
Posterior cingulate cortex (PCC)	2520
Left superior frontal gyrus (SFG_L)	7765
Right superior frontal gyrus (SFG_R)	7936

Table 2: Significant between group differences in mean connectivity (NP-CSF = Non pathological CSF, P-CSF = Pathological CSF)

Seed VOI	Target VOI	Group comparison	p
HIPP_L	LPC_R	NP-CSF > P-CSF	0.0258
HIPP_L	MTC_L	NP-CSF > P-CSF	0.0439
HIPP_L	SFG_R	NP-CSF > P-CSF	0.0019
HIPP_R	LPC_R	NP-CSF > P-CSF	0.0375
HIPP_R	SFG_R	NP-CSF > P-CSF	0.0155

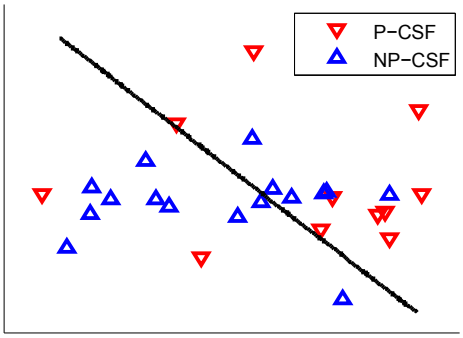

Figure 1: PCA showing the first two principal components of the full VOI-to-VOI connectivity data for all subjects (P-CSF = pathological CSF patients, NP-CSF = non-pathological CSF patients, black line = linear discriminator between groups)

Results: The VOI-to-VOI connectivity analysis revealed several differences between group averages using both the right and left hippocampus as seed VOI (Table 2). Of the observed mean connectivity differences, the MCI group with non-pathological CSF exhibited stronger connectivity than the MCI group with pathological CSF. PCA discrimination analysis reached a sensitivity of 81.8% and a specificity of 62.5%.

Discussion: In this work, the connectivity within the default mode network was investigated with respect to differences between patients diagnosed with MCI, who had non-pathological or pathological CSF biomarkers. The hippocampus showing reduced connectivity in the pathological CSF group with several target VOIs compared to the non-pathological CSF group indicates that patients with AD exhibit disturbed functional hippocampal connectivity already before dementia has developed. Altered hippocampal functional connectivity has previously been observed in group comparisons between healthy controls and patients with AD dementia [5]. Furthermore, linear discrimination analysis of principal components suggests that the full VOI-to-VOI connectivity information can be used as a classifier of the two sub groups. In summary, we have shown that resting state fMRI can be used to detect changes in functional connectivity within a group of MCI patients, differentiated by a combination of CSF biomarkers. To confirm our findings of changes in functional connectivity in the transition into AD, further work will be performed on a larger cohort of MCI patients and healthy controls.

References:

1. Hansson O, et al. *Lancet Neurology,* 5: 228-34, 2006.
2. Sheline Y, et al. *The Journal of Neuroscience*, 30(50): 17035-17040, 2010.
3. Greicius M, et al. *PNAS*, 101: 4637-4642, 2004.
4. Maldjian JA, et al. *Neuroimage*, 19: 1233-1239, 2003.
5. Zhou J, et al. *Brain*, 133: 1352-1367, 2010.