Resting state fMRI of the early stages of Alzheimer's desease

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Introduction

Functional connectivity in imaging refers to a descriptive measure of spatio-temporal correlations between distinct regions of the cerebral cortex [1]. Functional connectivity may also be extracted from spontaneous activity of the resting brain. During resting state, high temporal coherence of low-frequency (<0.08 Hz) fluctuations in fMRI time series has been observed between spatially distinct but functionally related brain regions [2]. The low-frequency fluctuations in MR signal intensity are supposed to arise from fluctuations in capillary blood flow and blood oxygenation, which are, at least partially, due to neuronal activity. The synchrony of low-frequency fluctuations implies that there is underlying functional organization of the brain [3]. In the early diagnosis of cognitive impairment, which involves a disconnection syndrome between dissociating neuronal systems, is crucial to consider the interaction between distinct cerebral regions. Recently, it has been shown that functional connectivity both within the Default Mode Network (DMN) [4] and between the right hippocampus and a set of regions [5] was disrupted in patients with Alzheimer's Disease (AD). In the present work, we compare low frequency correlation analysis obtained from patients with amnestic Mild Cognitive Impairment (a-MCI) and patients with AD to that obtained from an age-matched group of healthy subjects. The final goal is to identify specific patterns of low-frequency brain activity correlation increasing the diagnostic confidence in patients with early AD.

Methods

Six healthy subjects, five MCI and four AD (age ranging from 50 to 70yrs) were scanned on 3T scanner (Siemens, Erlangen, D). The protocol included 8min EPI (TR/TE=2080/30 ms, 32 Axial Slices AC-PC (2,5 mm thick, 1.25 mm skip), 3x3 mm^2, 64x64, 220 vol) at rest with eyes closed. Resting data were preprocessed using SPM5 (www.fil.ion.ucl.ac.uk/spm), to reduce scanner artifact, correct for head motion, and transform the data into a standard atlas space. The objective of the correlation analysis was to identify regions of cortex intrinsically correlated with either the hippocampal formation and two main regions of DMN, that are Anterior Cingulate Cortex (ACC) and Posterior Cingulate Cortex (PCC). The basic procedure consisted of computing, for all brain voxels, the correlation coefficient against the BOLD time series extracted from a particular seed region [3]. We computed correlation maps for Right Hippocampus (RH), Left Hippocampus (LH), PCC and ACC. The preprocessed functional data (in atlas space) were passed through an additional series of processing steps. Several sources of spurious or regional non specific variance were removed, slice by slice, by regression including: six parameters obtained by rigid body head motion correction, the signal averaged over the whole slice, the signal averaged over the cerebral spinal fluid and the signal averaged over the deep white matter. Then, for each voxel temporal filtering remove constant offsets and linear trends over each run while retaining frequencies in the 0.009- to 0.08 Hz band. Data were, finally, smoothed using 6-mm full-width half-maximum Gaussian blur. The correlation maps were converted to z values using Fisher's transformation [3].

Results

Fig A shows one sample t-test of ACC-driven correlation maps obtained from healthy subjects respect with those obtained from patients. The differential map indicates a change in correlation strength between ACC and LH. The plot in the inset suggests a severe decreasing trend from healthy controls (HC) to MCI together with AD patients. Fig B shows one sample t-test of PCC-driven correlation maps obtained from healthy subjects respect with those obtained from patients. As shown in the correlation strength plot, PCC to ACC functional connectivity seems to be slightly modulated from HC to AD patients.

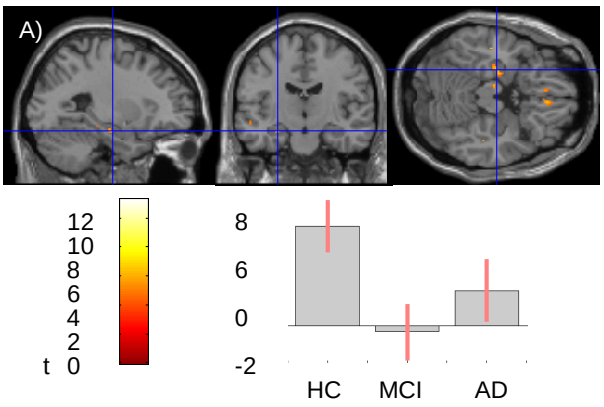

Fig A *One sample t-test of ACC-driven correlation maps obtained from healthy subjects respect with those obtained from patients. The inset shows the correlation strength between ACC and LH.*

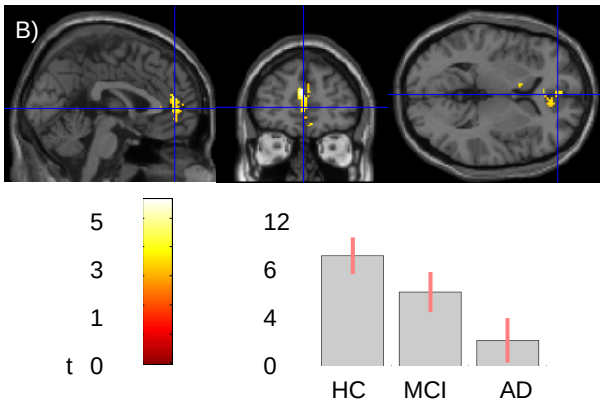

Fig B *One sample t-test of PCC-driven correlation maps obtained from healthy subjects respect with those obtained from patients. . The inset shows the correlation strength between PCC and ACC.*

Discussion

This work confirms previous results obtained in AD patients [4,5], showing a disruption of the PCC-ACC and LH-ACC connectivity. Our study suggests that a similar pattern of abnormalities is already present in patients with MCI, thus characterising the cognitive dysfunction occurring in AD pathology since its early stages. The reduced correlation of connettivity between hippocampal formations and ACC in both MCI and AD patients remarks the central role of the medial temporal structures in the evolution of the disease. Consistently with the idea of a continuum spectrum between normal aging and fully developed dementia, the changes observed were more severe in AD compared to MCI patients. This suggest the potential application of this technique to studies of monitoring the natural history of AD and clinical trials.

References: [1] Friston K et al. J Cereb Blood Flow Metab (1993); 13:5. [2] Biswal et al. Magn Reson Med (1995); 34:537. [3] Fox MD et al. Proc Natl Acad Sci USA (2005); 102:9673. [4] Greicius et al. Proc Natl Acad Sci USA (2004); 101:4637. [5] Wang L et al. NeuroImage (2006); 31: 496.