

DMN FUNCTIONAL CONNECTIVITY CHANGES PREVIOUS TO CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE

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Target audience: Scientists and clinicians interested in early diagnosis of cognitive impairments using resting state fMRI analysis.

Purpose: To analyze functional connectivity differences in the Default Mode Network (DMN) which are accompanied by structural changes in the hippocampus, in order to obtain early biomarkers for probable Mild cognitive impairment (MCI) and Alzheimer's disease (AD) development.

Introduction: Anatomical 3D T1 weighted images have been widely used to assess the volume and thickness of cortical and subcortical structures. It has been demonstrated that volume loss of hippocampi, entorhinal cortex and amygdala are early biomarkers for the diagnosis of cognitive impairments and AD¹. In this work, we investigate novel early AD biomarkers other than these ones.

Resting state fMRI analysis allows evaluating functional connectivity in resting state networks². Statistically significant connectivity differences in one of these networks, the DMN, have been reported between controls and patients with MCI or AD³.

We present here differences in the DMN functional connectivity between healthy subjects with significantly different normalized hippocampal volume (NHV), defined as the *hippocampal volume vs whole brain gray matter volume* ratio. The subjects are volunteers in the Vallecas Project, which is a longitudinal study that evaluates normal ageing in a cohort of more than 600 healthy elder people (ages between 70y and 85y). The prevalence (13%) of AD in people older than 65 years⁴ suggests that a certain number of those subjects will develop AD in the next years. Subjects with lower NHV are more prone to develop AD than the subjects with higher NHV. It has been reported that functional connectivity impairment is an early biomarker that precedes structural changes⁵. Based on it, our hypothesis is that subjects with lower NHV will present a lower functional connectivity.

Methods: *Subjects:* 632 healthy subjects (70-85 years) underwent a cognitive test to participate in this study. Initially we selected those subjects with abnormally small NHV, at least two standard deviations below the mean. This condition group included 25 subjects (16 females / 9 males; mean age 76±4years). The paired control group included subjects whose NHVs were greater than the mean NHV plus the standard deviation, in order to ensure that their hippocampi were preserved.

Data acquisition: MRI data were collected using a General Electric Signa 3.0 T MR Scanner. Resting-state functional images were acquired in a single run of 120 volumes, using a GE-EPI pulse sequence whose parameters were: TR=2.5s, TE=27.5ms, voxel dimensions=2.5x2.5x2.6mm, number of slices=32. Sagittal 3D T1 weighted images were acquired with: TR=10.024ms, TE=4.56ms, TI=600ms, NEX=1, acquisition matrix=288x288, full brain coverage, resolution=1x1x1mm, flip angle=12 parameters.

Stimuli and experiment: Subjects underwent closed eyes resting-state fMRI during 5 minutes.

Data preprocessing: Functional imaging preprocessing was carried out using FEAT from FMRIB's Software Library (FSL) and AFNI. The preprocessing steps were: despiking, slice timing correction, motion correction, fieldmap correction, spatial smoothing (FWHM=6mm) and temporal high pass filtering (100s). Hippocampus and grey matter volume estimations were performed with FreeSurfer.

Data analysis: FSL dual regression was applied to obtain the individual spatial maps related to the DMN spatial map reported by Smith et al.². Permutation statistics were computed with FSL randomize to evaluate differences between the two groups. The statistical analyses were considered significant for a p<0.005, threshold free cluster enhancement (tfce) corrected.

Results: Functional connectivity is decreased in DMN related areas in subjects with lower NHV versus those with higher NHV (Fig. 1). However, the opposite doesn't happen: no statistically significant increase in connectivity is found in subjects with lower NHV versus higher NHV. Differences in connectivity are found in posterior cingulate gyrus, right parietal lobe and occipital lobes.

Discussion & conclusions: A connectivity decrease in the DMN is statistically significant in subjects with a lower NHV, especially in the posterior cingulate gyrus, despite them being healthy elder people. Considering the hypothesis that these subjects are more prone to develop AD in the future, we have corroborated the reported idea^{3,5} that functional changes in the DMN are an early biomarker for AD, which happen, at least, at the same time as structural changes, or maybe even before, because no structural changes in DMN areas have been appraised yet in those subjects.

We conclude that the DMN connectivity is altered in individuals at risk for developing AD, likely representing effects of ongoing early neurodegeneration. This idea could be finally probed in some years. We are following the evolution of these subjects in a longitudinal study.

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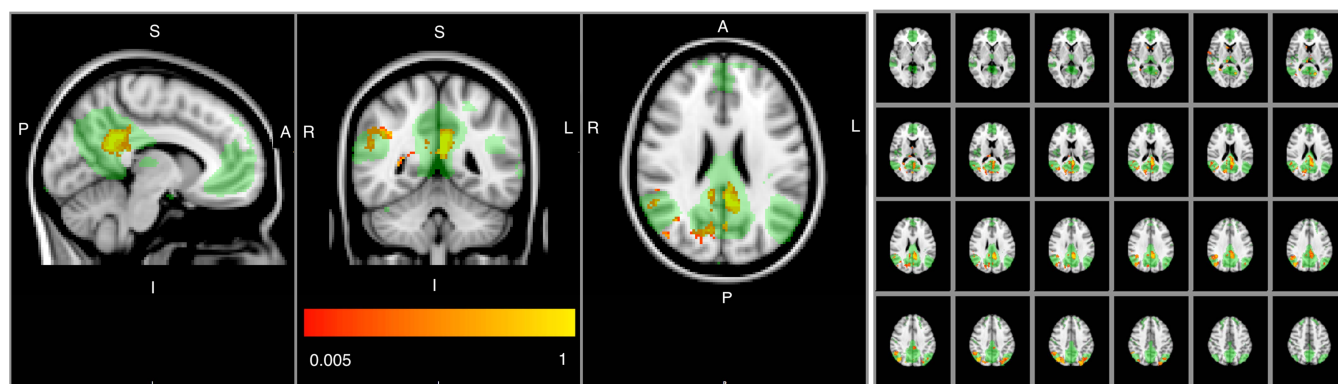


Figure 1: DMN related brain areas in which connectivity is decreased in subjects with lower NHV are shown in red-yellow (p < 0.005, tfce corrected). DMN spatial map template is shown in green (p < 0.05).