The role of the cerebellum in Alzheimer's disease cognitive decline: evidence from resting-state fMRI study

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INTRODUCTION

Alzheimer Disease (AD) is characterized by a progressive accumulation of brain tissue abnormalities that account for cognitive and behavioral manifestations by local damage and disconnection mechanism (1). Cerebellar atrophy, mainly localized in Crus I, has also been reported (ref). This cerebellar region is functionally connected with the association cortex, and is believed to take part in higher-level brain functions. In light of these evidences, we used here resting-state functional MRI (RS-fMRI) to assess modifications of functional connectivity (FC) between the cerebellum and the rest of the brain in patients with AD. We focused our analysis on the Dentate Nucleus (DN), which is the sole cerebellar output channel, to test the hypothesis that changes in FC between the DN and the association cortex might account for the cognitive deficits typically observed in AD, such as memory disorders.

METHODS

Seventy-eight patients with AD (mean/SD:73.5/6.4) and 58 healthy subjects (HS) (mean/SD:64.7/8.7) were recruited for this study. *MRI acquisition at* 3T (Magnetom Allegra, Siemens, Erlangen, Germany): 3D modified driven equilibrium Fourier transform (MDEFT) and 220 fMRI volumes collected with T2* weighted echo planar imaging (EPI) sensitized to blood oxygenation level dependent imaging (BOLD) contrast. *MRI preprocessing and statistical analysis.* RS-fMRI data were pre-processed using SPM8 (Wellcome Department of Imaging Neuroscience; http://www.fil.ion.ucl.ac.uk/spm/). A seed-based approach was used. The left and right DN masks were separately extracted according to the spatially unbiased atlas template of the cerebellum and the brainstem (2) (see Figure 1) and resliced in EPI standard space. The mean time course of the voxels within each ROI was used as a regressor in a 1st level SPM analysis while at second level, a two-sample t-test model was used to explore differences in connectivity between AD and HS ($p<.05$, FWE at cluster level). *Neuropsychological assessment.* Memory performances were evaluated in 36 out of AD patients (MMSE: <24) (3) (mean-age /DS: 73.7/3.6) and 32 controls (MMSE: >24) (3) (mean-age /DS: 68.8/6.8) using the following tests:Rey-Osterrieth Complex Figure Test (copy and recall) (4) to analyze visuospatial long term memory ; Short story test (immediate recall) (5) and Rey's 15 mots short term (immediate recall) (6) to analyse short term verbal memory; Rey's 15 mots long term (delayed recall) (6) to analyse long term verbal memory. Individual raw scores were converted in Z-scores and a mean Z-score was obtained for each test to evaluate patients' memory perfomances. The distribution of variables was tested by Shapiro-Wilk test and non-normal distribution correlations between memory scores and FC value in AD patients were performed by Spearman's Test.

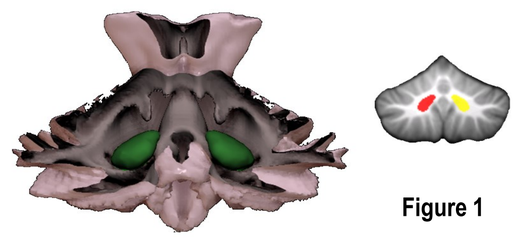

Figure 1

RESULTS

Functional connectivity

When compared to HS, AD patients showed a selective increase in FC between the left DN and different regions in the right temporal lobe, such as the inferior temporal pole and superior temporal gyrus, the right temporo-occipital pole and lateral occipital cortex (FWE 0.05) (See figure 2).

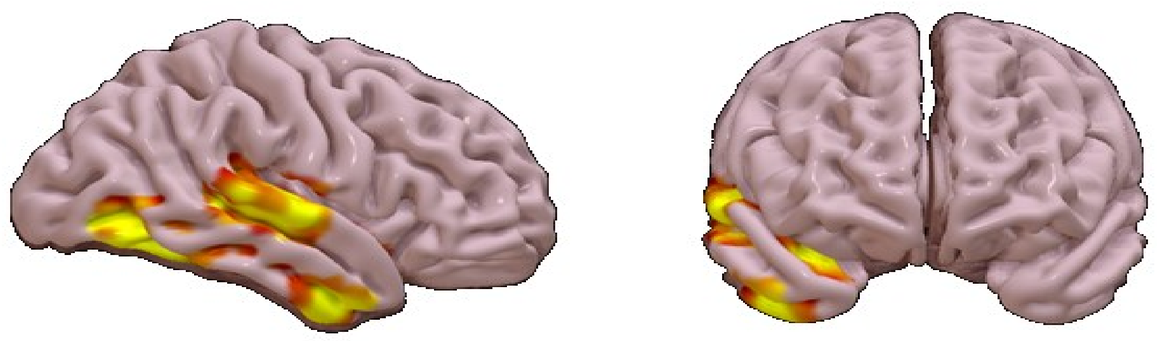

Figure 2

Behavioral correlations

AD patients had negative z-scores in all tests (see figure 3). The Spearman's correlations coefficients revealed a pattern of negative correlations between memory scores and cerebral regions of increased FC with the left DN. In particular, a negative correlation was found between short-term verbal and long-term visuospatial memory scores and FC values in the right superior temporal gyrus, and long-term episodic memory scores and FC values in the temporo-occipital fusiform cortex.

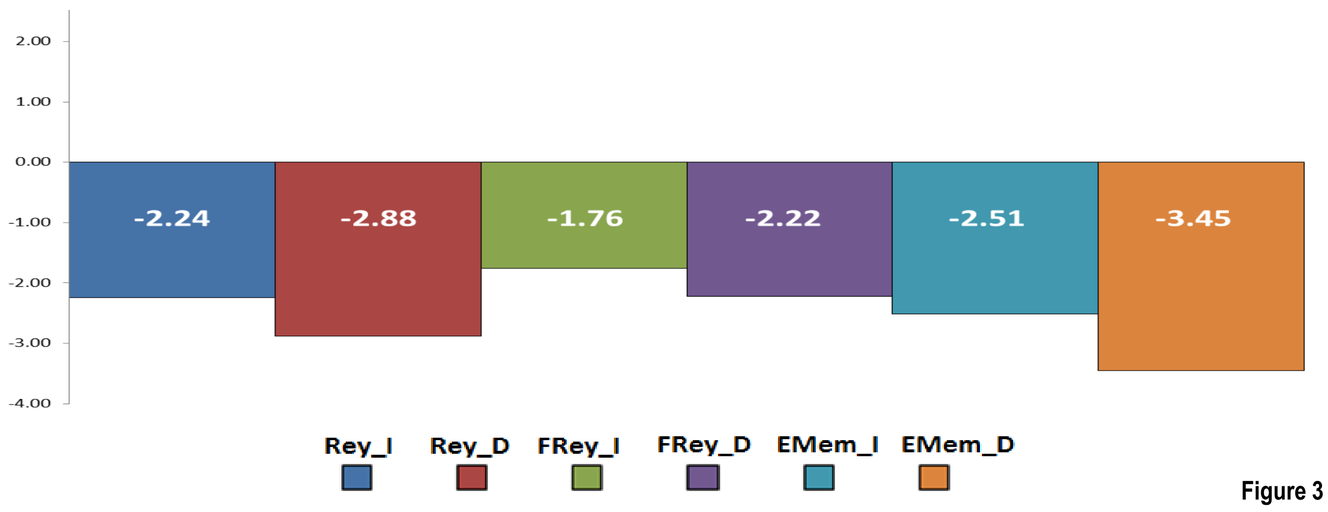

Figure 3

CONCLUSION

This study demonstrates a selective pattern of increased FC between the left DN and the right temporal lobe in patients with AD. This cortical region, in AD brains, is known to be critically involved in determining verbal and non-verbal episodic memory impairment, topographical disorientation, progressive prosopagnosia, and deterioration of semantic knowledge about famous people (7). According to this evidence, the negative correlations between memory scores and FC values in the right temporal pole suggest that lower memory performances are related to increased connectivity of the DN with this cerebral region. Together with previous findings of cerebellar atrophy in AD, the pattern of increased FC we found here suggests a release of the inhibitory control which is normally exerted by the cerebellar cortex on the DN. As a consequence, this might result in an increase of the DN excitatory output that, via cerebello-thalamo-cortical pathways, might contribute to the cortical brain dysfunction in areas critically implicated in determining AD symptoms.

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