Alterations of resting state networks in dementia: reduction of functional integrity and compensatory mechanisms

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Target Audience: Clinicians and researchers who are interested in Dementia and in resting state fMRI applied to clinical studies.

Purpose: Over the years Resting State functional MRI (rs-fMRI) has shown a great potential to study and characterize the signs of neurodegeneration at different stages of the Alzheimer's disease (AD). Several works addressed the changes in functional connectivity of the brain due to disease and demonstrated that the default model network (DMN) of AD subjects is affected by the pathology: functional connectivity in patients was decreased with respect to healthy subjects.[1,2] However, only a few studies have investigated in detail which and how many brain networks are affected by the disease and what is the dynamic of alteration throughout the pathology evolution, from mild cognitive impairment (MCI) state to the AD condition.[3]

The purpose of this study was to assess, by means of rs-fMRI, which resting state networks (RSN) are interested by the disease at different stages. In particular our effort has been focused on investigating the possible dynamics of corruption of the RSNs when comparing AD subjects with MCI ones and healthy controls.

Methods: MRI acquisitions: 18 subjects (12 females, mean age 69.8± 6.6) affected by AD with a Mini Mental State Examination (MMSE) score ≤ 24, and 20 subjects (12 females, mean age 72.7± 5.4) with MCI (24<MMSE<30) underwent MRI examination using a 1.5 T MR Philips Intera Gyroscan (Philips Healthcare, Best, The Netherlands) with an 8-channel head coil. In order to obtain a reference metric for our findings 18 healthy subjects (13 females, mean age 69.1± 5.5) were also scanned. For each subject a functional MRI (rs-fMRI) FE-EPI protocol was acquired with TR/TE=3000/60 ms, voxel size=2.2x2.2x4 mm^3, FOV=250x250 mm^2, SENSE factor=3.1, for a total of 100 volumes (26 slices each).

fMRI analysis: for each subject included in the protocol rs-fMRI images were analysed using the Independent Component Analysis (ICA) computational method in order to characterise RSNs. ICA analyses were carried out using MELODIC from the FMRIB Software Library (FSL,[4] version 4.1.9). A non-parametric permutation test (dual regression technique) was then applied to create and compare group-specific maps for each independent spatial component. In particular we used the dual regression algorithm, as implemented in FSL, set with 1000 permutations, in order to detect statistically significant differences between the groups within the MELODIC maps. Statistical maps were family-wise error (FWE) corrected applying threshold-free cluster enhancement (TFCE). A statistical threshold of $p \leq 0.05$ was considered significant.

Results and Discussion: Group ICA analysis resulted in 25 independent components of which 12 were recognized as part of 8 RSNs. Three major findings are coming out of this study: **1)** Overall, our results confirm a widespread *corruption* of the cerebral resting state networks between the patients (MCI and AD) and HC, involving auditory cortex, executive control, DMN, sensory cortex, cerebellum and visual system[3]. In particular we found a significant reduction ($p \leq 0.05$, corrected) for AD, compared with HC group, in the prefrontal cortex (superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus and precentral gyrus) in the networks of the auditory system, executive control (also in frontal orbital cortex and frontal operculum cortex) and in the sensory-motor system. Significant reductions ($p \leq 0.05$, corrected) in prefrontal cortex were also found for the MCI group, compared with controls, in the dorso-visual steam networks, sensory-motor system and the medial visual cortical areas. The analysis of the DMN revealed a gradual reduction in functional connectivity for AD patients in the cuneus, precuneus and posterior cingulate cortex areas, which did not reach significance ($p=0.16$) when compared with HC. 2) Considering the pathology state (i.e. separating MCI from AD), a part from those involving the cerebellum, all the RSNs present a gradual *reduction* of the functional connectivity, which correlate with the seriousness of the pathological state (AD are worse than MCI that are worse than HC). **3)** Furthermore, our findings suggest that RSNs involving areas of the cerebellum and of the contralateral frontal lobe, present an abnormal behaviour for AD and MCI subjects, if compared to HC. In particular, we found that, in the dorsal-visual stream (DVS), patients present a level of functional connectivity, which is gradually *increased* from HC to MCI and AD subjects in specific areas of the cerebellum (Crus I, Crus II, Left VI) and in the contralateral frontal lobe. This abnormal behaviour was mostly evident for AD and MCI in the Left DVS network connecting the right cerebellum (right crus I, right crus II) with the contralateral frontal lobe (Fig.1). The Right DVS network also showed an increased functional connectivity, but only for the MCI group, when compared to HC, both in the left cerebellum (left crus I, left crus II, left VI) and in the contralateral frontal pole (Fig.2). These last findings could be interpreted as a potential compensatory mechanism to functional disorders caused by the disease [3], increasing the functional activity of specific areas in response to a gradual cognitive decline.

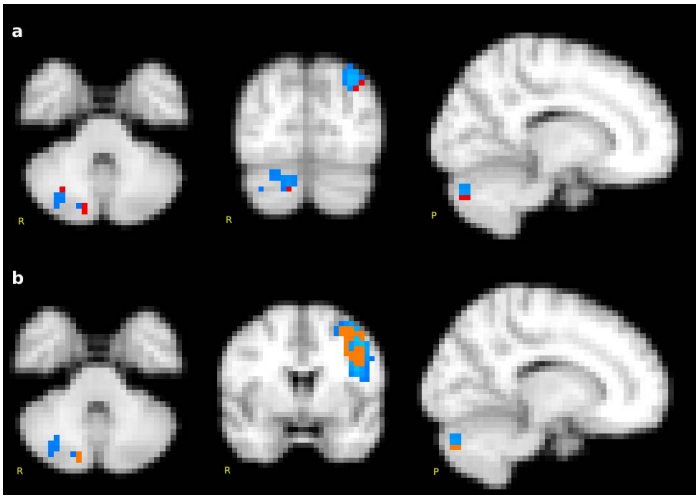

Fig.1: Left Dorsal-visual stream (DVS) network (light blue). (a) increased functional connectivity (red) for AD, compared to HC, in the right cerebellum (right crus I, right crus II) and in the contralateral frontal lobe (precentral gyrus, inferior frontal gyrus, middle frontal gyrus). (b) increased functional connectivity (orange) for AD, compared to HC, in the right cerebellum (crus, vermis) and in the contralateral frontal lobe (precentral gyrus, inferior frontal gyrus, middle frontal gyrus).

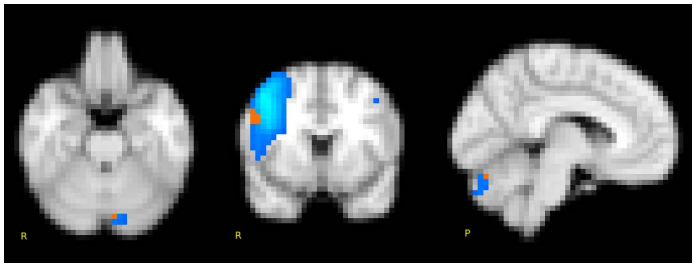

Fig.2: Right Dorsal-visual stream (DVS) network (light blue); increased functional connectivity (orange) for MCI group, compared to HC, in the left cerebellum (left crus I, left crus II, left VI) and in the contralateral frontal lobe (precentral gyrus, inferior frontal gyrus, middle frontal gyrus).

Conclusions: Our results confirm that rs-fMRI can reveal changes in specific RSNs that are indicative of neurodegeneration and are compromised at different levels depending on disease severity. The data also show that there are changes in the RSNs involving the cerebellum, which could been explained as abnormal recruitments of neurons. These changes could have a compensatory meaning leading to increase activity in specific cerebro-cortical areas, along with the worsening of the pathology. Future work will investigate structural abnormalities and the presence of atrophy.

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References: [1] Wu Xet al. (2011) Hum Brain Mapp 32(11):1868-81. [2] Koch W et al.(2012) Neurobiol Aging 33(3):466-78. [3] Binnewijzend MA et al. (2012) Neurobiol Aging 33(9):2018-28. [4] FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl