

Resting-state fMRI contributes to differentiate patients with dementia with Lewy bodies from those with Alzheimer's disease

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Background and Objective. Functional Magnetic Resonance Imaging (fMRI) can be used *in vivo* to detect synchronous fluctuations in blood oxygenation level-dependent (BOLD) signal across the brain at rest. This technique, which is known as resting state fMRI, is traditionally used to investigate functional connectivity (FC) within well defined resting-state networks (RSNs), such as those related with sensory-motor, visual, auditory and cognitive functions. Abnormal connectivity within specific RSNs can provide useful information on the pathophysiological events underlying several neurological disorders [1]. Functional brain organization is known to be disrupted in the presence of Alzheimer's disease (AD). Brain disconnection, together with regional grey matter loss, has been recently recognized as a major factor contributing to the development of cognitive disabilities in patients with AD [2]. Previous RS-fMRI studies have already reported a selective disruption in FC between prefrontal and parietal regions within the so-called default mode network (DMN) in AD [3,4]. Dementia with Lewy Bodies (DLB) has been recognized as the second most common form of cognitive decline in western world populations [5]. However, the differential diagnosis between DLB and AD remains a challenging issue for clinicians. Although the application of consensus criteria for clinical diagnosis of DLB [6] has shown high specificity, a relevant percentage (ranging from 17 to 78% of cases) of missed diagnoses is still reported [7]. To our knowledge, there are no previous studies that used RS-fMRI to directly compare changes in functional brain connectivity between patients with AD and those with DLB. On the basis of their different pathophysiologies, this study aimed at assessing whether there are specific patterns of functional brain disconnection for the two principal forms of dementia, AD and DLB.

Subjects and Methods. So far, we recruited 33 patients with AD [8]. [M/F ratio=16/17; mean (SD) age=73.45 (7.6) years] and 14 patients with DLB [9] [M/F ratio=10/6; mean (SD) age=75.5 (6.3) years], who underwent a clinical and neuropsychological examination, and MRI at 3T (Siemens Allegra system). Seventeen healthy subjects were also recruited as controls [M/F ratio=15/2; mean (SD) age=62.82 (9.1) years]. The MRI acquisition protocol included: 1) dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); 2) fast-FLAIR (TR = 8170 ms, TE = 96 ms); and 3) a 8 minute resting-state BOLD acquisition (gradient echo EPI, TE=30ms, TR=2.08). Dual-echo and FLAIR images were used to exclude the presence of any macroscopic abnormality in every subject. Functional data preprocessing was performed with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>), after discarding the first 4 volumes. Images were realigned, corrected for slice-time, normalized into Montreal Neurological Institute (MNI) space, and smoothed with a 8mm³ Gaussian kernel. Finally, all images were filtered by a phase-insensitive band-pass filter (pass band 0.01–0.08 Hz) to reduce the effect of low frequency drift and high frequency physiological noise. Due to excessive motion, thirteen AD and eight DLB patients were excluded from functional connectivity analysis. A model-free analysis was employed by using independent component analysis (ICA) implemented in the GIFT package, in order to allow for a simultaneous separation into individual components. A second level analysis was performed on the resulting images using a full-factorial model in SPM5.

Results. Among the 20 components estimated by ICA, ten RSNs, already reported by others [10], were identified (default-mode, core, parietal, medial frontal cortex, primary visual, temporal, auditory, sensory-motor and both left and right hemisphere networks). So far, the second level analysis has been performed with respect to the RSNs likely to be affected in both pathologies (AD and DLB). Between-group differences, therefore, were investigated for the default-mode, parietal, medial frontal cortex, and primary visual networks. Overall, AD and DLB patients showed less significant FC, compared to the healthy controls. Within the default-mode network, AD patients showed a decreased connectivity in the posterior cingulate cortex/precuneus (PCC/precuneus) bilaterally (p-corr. = 0.003) (figure 1). Conversely, when analyzing the visual RSN, DLB patients showed a well localized reduction of FC in the occipital cortex (p-corr. = 0.002) (figure 2). Finally, within the medial frontal cortex RSN, patients with AD showed a decrease of FC within the right insula (p-corr. <0.001).

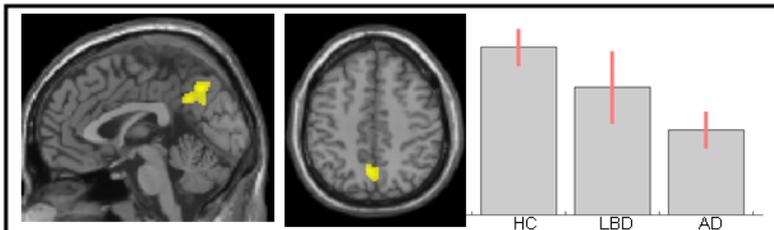


Fig 1. Decreased positive correlation with the precuneus, within the default-mode network, in AD patients compared with healthy controls. The plot shows the BOLD signal changes in the precuneus. The activation map is rendered at a threshold of p-corr. = 0.003, at the cluster level. Any significant differences was observed between HC and LBD patients.

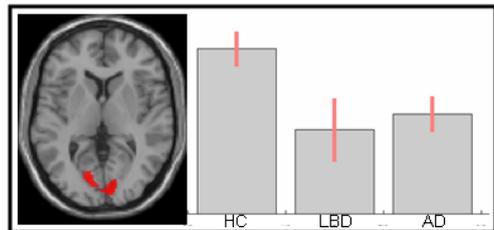


Fig 2. Significantly decreased correlation with the cuneus, within the visual network, in LBD patients, compared with healthy controls. The plot shows the BOLD signal changes in the cuneus (p-corr. = 0.002).

Discussion. Our study provides new evidence of disrupted organization of functional brain networks not only in patients with AD, but also in those with DLB. Consistent with previous reports, the default mode network was specifically affected by AD pathology, with a selective reduction of FC in the PCC/precuneus. This finding suggests that structural disconnection between this area and the medial temporal lobe structures are critical in AD evolution. Consistently, atrophy in medial temporal lobes is predominant in AD but not in DLB patients [11]. On the other hand, a selective reduction of FC in the occipital cortex (within the visual RSN) supports the idea that abnormalities in this region might account for the presence of visual hallucinations [12], which are a distinctive feature for DLB, and a relatively rare manifestation in AD. These results, however, should be regarded as preliminary given the small number of subjects in the DLB group.

In conclusion, this study confirms that RS-fMRI represents a useful tool for pathophysiological investigation in dementias, and might provide biomarkers of diagnostic value to increase the confidence of a correct and early identification of patients with AD and patients with DLB.

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