Structural and functional connectivity in Dementia with Lewy Bodies compared to Alzheimer Disease

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Purpose: Dementia with Lewy Body (DLB) is the second most common cause of degenerative dementia after Alzheimer Disease (AD)[1]. AD and DLB share many similar symptoms and this usually causes delayed or incorrect diagnosis. Amongst available in vivo biomarkers offered by neuroimaging techniques, characterizing how brain regions are interconnected has the potential to support an accurate diagnosis identifying differences in brain connectivity between different types of neurodegenerative dementias. We aimed at detecting dissimilarities between AD and DLB's connectivity, using a multimodal approach to study the impact of these diseases on both structural and functional connectivity. We focused on two different white matter tracts, namely the inferior frontal occipital fasciculus (IFOF) and the superior cingulum bundle (sCI) and two functional networks (FNs) whose involvement in different forms of dementia has not been clarified yet. Nevertheless, these FNs are likely to be critical for functions such as attention differently impaired in DLB and AD patients.

Methods: 76 right-handed participants, consisting of 45 patients with cognitive dementia meeting the diagnostic criteria for probable AD (n = 32) and for probable DLB (n = 13) and a group of healthy controls (HCs, n= 31) were enrolled in the study. Each participant underwent an MRI session and an extensive neuropsychological protocol. All neuroimaging data here reported were obtained using a head-only 3.0 T MR scanner (Siemens Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany), equipped with a circularly polarized transmit-receive coil. The MRI protocol included conventional MRI acquisitions and 8 minutes of resting-state fMRI (gradient echo EPI, TE=30ms, TR=2.08). **fMRI preprocessing:** functional data pre-processing was performed using SPM8 (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 8mm^3 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. **fMRI analysis:** a model-free analysis was employed by using the 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 one-way ANOVA model in SPM8. In the ANOVA model two different comparisons were performed for each fronto-parietal network (left and right; see Fig 1): 1) A comparison of HCs with AD and DLB (HS > AD; HS > DLB; HS < DLB; HS<AD); 2) A direct comparison of AD with DLB (AD > DLB; AD<DLB). Differences were considered as significant at p-values <0.05, after FEW correction at cluster-level . Additionally the acquisition protocol included a DTI sequence (single-shot EPI, no. of diffusion directions=61, with 7 b0 images, max b factor = 1000 s.mm^{-2}; TE=85 ms, isotropic resolution=2.3 mm^3). **DTI processing:** FA and MD, were computed from the diffusion tensor (DT) fitted with weighted linear least-square in Camino[2], after correction for head movements and eddy currents based on affine registration to the first b0 volume with FSL. **DTI analysis and tractography:** The WM tracts (Fig.2) were reconstructed with multi-fiber probabilistic tractography carried out using 10000 iterations of the probabilistic index of connectivity (PICo) algorithm[3] applied to fiber orientation distribution functions estimated with PAS-MRI[4]. A between-subject ANOVA was performed for the 2 groups of patients and HS, adjusting for age, education and cognitive state.

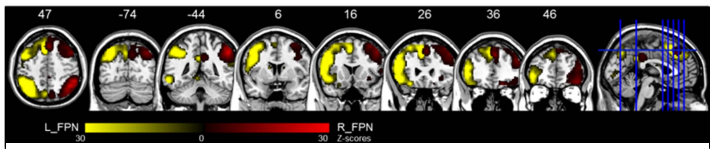

Fig. 1. Abbreviations: L_FPN; R_FPN=left and right fronto-parietal network. The fMRI data displayed on the coronal, axial and medial sagittal brain surface show the activation map associated with the two networks of interest. Specifically the L_FPN is represented in yellow and R_FPN in red.

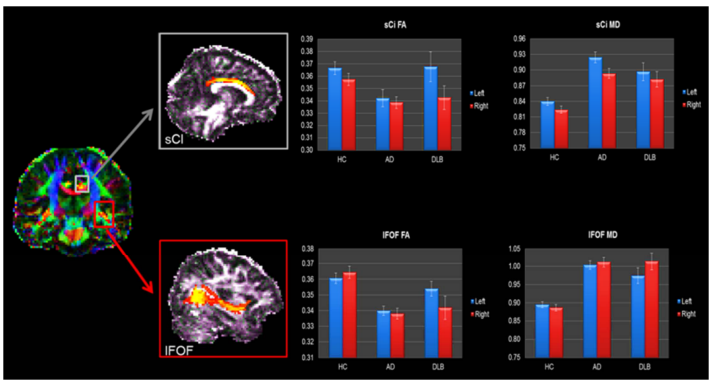

Fig. 2. On the left, the coronal brain surface shows colors of the tracks indicating the local fiber orientation (red: left-right, green: dorsal-ventral, blue: cranial-caudal; see colored arrows). On both the coronal and sagittal brain planes the sCI and the IFOF are represented in a yellow-red activation map. On the right the pattern of the FA and MD are showed separately for the left (blue bars) and for the right (red bars) hemispheres.

Results. fMRI data: comparing patients' connectivity in FNs to HCs, a decreased functional integration was recorded in AD group as compared to the HCs in middle temporal lobe, while a decreased functional connectivity was shown in the right medial frontal cortex in DLB group with respect to HCs. Comparing DLB to AD patients, a significant decrease of functional connectivity in the AD group was found in the left fronto-parietal network, specifically in the left medial frontal cortex. **DTI data:** Considering the mean FA in sCi a group x side interaction was characterized by a significant reduction of left sCi's FA in AD group compared to HCs and DLB, while in the right sCI a significant FA reduction in AD group compared to HCs was documented, but also a trend of decreased FA in DLB compared to HCs. A group by side interaction was recorded also in the IFOF's FA. Post-hoc analysis showed in left IFOF a significant increase of FA in DLB group compared to AD, while only the AD group showed a significant reduction compared to HCs, indeed no significant difference was recorded between HS and DLB. Conversely, For the mean FA in the right IFOF no significant difference was recorded between AD and DLB, while a significant difference was recorded comparing both groups of patients with HCs. The mean diffusivity did not show difference between two groups of patients.

Discussion. Our results suggest that IFOF damage plays a pathophysiological role in dementias, as demonstrated by FA data, showing a bilateral pattern of abnormalities in AD and a unilateral pattern in DLB. A similar pattern of anisotropy was recorded in sCI. Interestingly, comparing AD to DLB patients a significant reduction of connectivity was recorded in the left hemisphere, and specifically in the left medial frontal cortex. Together with the tractography data, these results support the hypothesis of altered connectivity in the left hemisphere of AD patients compared to DLB.

References.

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