Inter and intra network connectivity predicts the evolution of MCI over time and the conversion from MCI to AD

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PURPOSE. Patients with amnestic mild cognitive impairment (aMCI) have higher probability to convert to Alzheimer's disease AD[1] than elderly controls. Previous studies have shown that patients with AD may have altered functional connectivity between different brain regions. Different resting state (RS-fMRI) networks interact with each other in determining higher level functions and dysfunctions[2]. Whilst disruptions of both intra and inter-network connectivity has been already described in AD patients[3], its prognostic role in determining which MCI patients will convert to AD has to be yet explored. The objective of this study is to explore whether intra- and inter-network functional connectivity in RS-fMRI networks can predict the conversion from MCI to AD. Five RS-networks were isolated according to a priori hypotheses on the cognitive profile typically observed in AD patients: the Default mode network, DMN; salience network, SN; executive network, ExN; and right and left fronto-parietal networks, rFP and lFP.

MATERIAL AND METHODS. 25 patients with aMCI and 28 healthy controls (HC) were enrolled for this study. Patients were reviewed after 1 year to assess whether they had converted to AD or remained stable. All patients underwent an MRI examination at 3T (Magnetom Allegra, Siemens, Erlangen, Germany), including the following acquisitions: Dual-echo turbo spin echo (TSE) (repetition time [TR]= 6,190msec, echo time [TE]= 12/109 msec); 2) fast-FLAIR (TR= 8.170 msec, TE= 96 msec, TI= 2.100 msec); 3) 3D Modified-Driven-Equilibrium-Fourier-Transform (MDEFT) scan (TR=1338 ms, TE=2.4 ms, Matrix=256x224x176, in–plane FOV=250x250 mm2, slice thickness=1 mm); 4) T2* weighted echo planar image (EPI) sensitized to blood oxygenation level dependent imaging (BOLD) contrast (TR: 2080 ms, TE: 30 ms, 32 axial slices parallel to AC-PC line, matrix: 64x64, pixel size: 3x3 mm2, slice thickness: 2.5 mm, flip angle:70°) for RS fMRI. BOLD EPI was collected during rest for a 7 min and 20 s period, resulting in a total of 220 volumes. During this acquisition, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. **RS processing:** The preprocessing steps included correction for head motion (using the standard realignment algorithm in SPM8), compensation for slice-dependent time shifts, and co-registration with the corresponding T1-weighted volume (MDEFT). The MDEFT was segmented using the segmentation algorithm is SPM8, and the resulting grey matter (GM) images were used to compute every subject's total GM volume. EPI 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. Group Independent Component Analysis (ICA) fMRI Toolbox[4] was used for independent component decomposition to identify 20 independent components[5]. **Intra-network analysis**: A full-factorial design was adopted to explore differences between MCI patients and HC. A flexible-factorial design was used to evaluate the Time (T0, FUP) x Group (MCIconv,MCIstab) interaction. GM volume was used as covariate of no interest. **Inter-network analysis**: Subject specific network time courses were detrended and pairwise correlated by Pearson's correlation, following an established procedure[6]. We computed the constrained maximal lagged correlation between pair-wise combinations of networks. Correlation coefficients were transformed to z-scores using Fisher's z-transformation and entered into a within subject ANOVA ($p < 0.05$, Bonferroni-corrected for multiple comparisons).

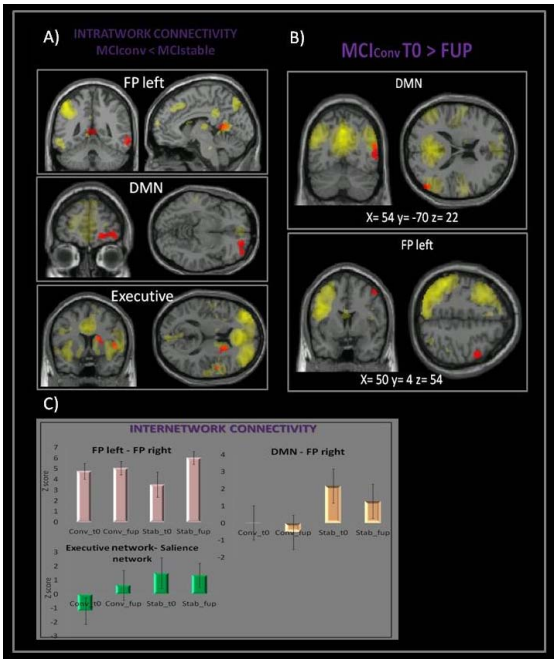

Figure 1. A) Decrease in FC in MCIconv vs. MCIstable at baseline in the lFP, DMN and ExN. B) Decrease in FC in MCIconv over time in DMN and lFP networks. C) Inter-network connectivity between different networks changes over time (lFP-rFP), and is decreased in MCIconv vs. MCIstable (DMN-rFP; ExN-SN).

RESULTS. After 1 year, 12 aMCI remained stable (MCIstable) and 13 converted to probable AD (MCIconv). **Intra-network results:** When compared to HC, MCI patients (converters, stable) reported no sign of FC alteration in any of the considered networks. When compared to MCIstable, MCIconv reported a reduced FC within the lFP network (posterior cingulated gyrus), within the DMN (left frontal lobe) and ExN (anterior cyngulate gyrus) (Figure 1A). Moreover, MCIconv reported a decreased connectivity over time within the DMN (lateral parietal lobe) and lFP (right precentral gyrus) network (Figure 1B). **Inter-network analysis:** A main effect of the factor Time emerged when evaluating the connectivity between FP left and FP right, with a general increase in the FC between the two networks independently of the group. Conversely, MCIconv reported lower inter-network FC between DMN and lFP and between EXN and SN, when compared to MCIstable.

DISCUSSION. Beyond the specific role of each single networks in specific cognitive functions, interactions between them are likely to better account for complex symptoms and for their appearance across AD evolution. Here, we report that both inter and intra network functional connectivity can predicts already at baseline which MCI patients will convert to AD at follow-up. Overall, our data confirm the validity of the RS fMRI in spotting pathophysiological dysfunctions in MCI patients and its evolution in time.

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