Combined functional and tractography connectome to investigate Alzheimer brain networks

Fulvia Palesi[1,2], Gloria Castellazzi[2,3], Elena Sinforiani[4], Paolo Vitali[5,6], Claudia A. M. Wheeler-Kingshott[7], and Egidio D'Angelo[2,6]

[1]Department of Physics, University of Pavia, Pavia, PV, Italy, [2]Brain Connectivity Center, C. Mondino National Neurological Institute, Pavia, PV, Italy, [3]Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, PV, Italy, [4]Neurology Unit, C. Mondino National Neurological Institute, Pavia, PV, Italy, [5]Brain MRI 3T Mondino Research Center, C. Mondino National Neurological Institute, Pavia, PV, Italy, [6]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, PV, Italy, [7]NMR Research Unit, Department of Neuroinflammation, Queen Square MS Centre, UCL Institute of Neurology, London, England, United Kingdom

Target Audience: Clinicians and physicists with an interest in brain structure and function.

Purpose: Several resting-state functional MRI (rs-fMRI) studies have revealed a generalized alteration of the resting state networks (RSNs) in patients affected by Alzheimer's disease (AD) and mild cognitive impairment (MCI) with particular interest to the default mode network (DMN)[1]. Functional brain alterations have been investigated both using an independent component analysis (ICA) [1] but also using a small-world approach based on graph theory[2]. Nevertheless only few studies have focused on the interaction between functional and structural connectivity from a "connectome" point of view[3]. We studied brain networks (BNs) from a structural point of view combining probabilistic tractography and a small-world approach on published rs-fMRI ICA results on a cohort of AD, MCI and healthy controls (HC)[4]. We aimed at assessing the structural brain proprieties strictly connected with brain functions and as such the main purpose of this study was to investigate structural alterations inside networks that were found to be functionally impaired by the pathology in a previous fMRI study on the same cohort of subjects [4].

Methods: Subjects: 14 AD (mean age 71 yrs, 10 females) with a mean Mini-Mental State Examination (MMSE) score equal to 20, 12 MCI (3 amnestic, 9 non-amnestic, mean age 74 yrs, 8 females, MMSE=24) and 16 HC (mean age 69 yrs, 12 females, MMSE=28) underwent MRI examination using a Philips Intera Gyroscan 1.5T MRI scanner (Philips Healthcare, Koninklijke, Netherlands) with an 8-channel head coil. MRI acquisition: 1) rs-fMRI FFE-EPI as in Castellazzi et al. [4]. 2) DTI single-shot SE-EPI with TR = 11.8 s, TE = 70 ms, 60 axial slices, FOV = 224 mm, 2.5 mm isotropic voxel and 15 non-collinear diffusion directions with b = 900 s/mm^2. 3) High-resolution 3D sagittal T1-weighted (3DT1w) FFE with TR/TE = 8.6/4 ms, flip angle = 8°, FOV = 240 mm, slice thickness = 1.2 mm, in-plane resolution = 1.25×1.25 mm^2 and 170 slices. rs-fMRI and DTI preprocessing (FSL[5]): In a previous work,[4] RSNs were compared among groups to create group-specific maps for each independent RSN in MNI space. DTI data were analysed by performing eddy current correction, brain extraction, diffusion indices maps creation and realignment to the 3DT1w volume using an affine transformation (12-d.f. FLIRT). 3DT1w images were normalized to the MNI152 template by using a non-linear transformation (FNIRT, FSL). RSNs found to be the most discriminant among groups from a functional point of view were transformed, by inverting the normalization procedure, into the individual DTI space. BNs analysis: Each impaired RSN was investigated as an individual BN. For each subject *nodes* of the BNs were identified with the distinct clusters of the analogous RSNs. Probabilistic tractography (FSL) was performed between each pair of nodes in the HC. All tracts were normalized in MNI152 space and a mean, thresholded (at 60% of HC) tract was generated for each pair of nodes. These tracts were transformed into the DTI space for each subject and were defined as *edges* of the BNs. Mean fractional anisotropy (FA), mean (MD), radial (RD) and axial diffusivity (L1) values were used to calculate the weight of each element of the connectivity matrices (=edge). Global efficiency (*Eglob*), strength and local efficiency of each node, were calculated for each BN[6]. A standard one-way ANOVA test ($p \leq 0.05$) with Bonferroni correction for multiple comparisons was performed.

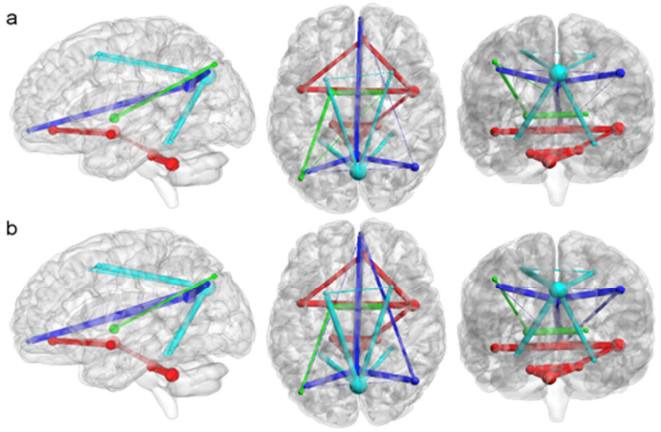

Figure 1: *3D brain networks representation from a sagittal, axial and coronal point of view. Nodes size is proportional to nodal degree, while edges size is proportional to their strength. Each colour represents a different RSN: AIN is red, BGN is green, functionally reduced DMN (in AD) is light blue and functionally increased DMN (in AD) is blue. a) BNs in HC. b) BNs in AD.*

		MD		L1		RD	
Network	**Group**	**Eglob**	**Strength (×10^{-2})**	**Eglob**	**Strength (×10^{-2})**	**Eglob**	**Strength (×10^{-2})**
AIN	**HC**	0.08 (0.01)	0.21 (0.01)	0.09 (0.00)	0.29 (0.01)	0.07 (0.01)	0.17 (0.01)
	AD	0.09 (0.01)	0.22 (0.01)	0.09 (0.00)	0.30 (0.01)	0.08 (0.00)	0.18 (0.01)
	p-value	--	--	--	--	--	--
BGN	**HC**	0.15 (0.01)	0.12 (0.01)	0.17 (0.01)	0.17 (0.01)	0.14 (0.01)	0.10 (0.01)
	AD	0.16 (0.01)	0.13 (0.01)	0.18 (0.01)	0.18 (0.01)	0.15 (0.01)	0.11 (0.01)
	p-value	0.040	0.040	0.014	0.015	--	--
DMN	**HC**	0.14 (0.01)	0.14 (0.01)	0.15 (0.01)	0.20 (0.01)	0.12 (0.01)	0.11 (0.01)
	AD	0.15 (0.01)	0.15 (0.01)	0.16 (0.01)	0.21 (0.01)	0.13 (0.01)	0.12 (0.01)
	p-value	0.010	0.010	0.008	0.008	0.015	0.014
DMNr	**HC**	0.12 (0.01)	0.16 (0.01)	0.14 (0.00)	0.24 (0.01)	0.11 (0.01)	0.13 (0.01)
	AD	0.13 (0.01)	0.17 (0.01)	0.14 (0.01)	0.25 (0.01)	0.11 (0.01)	0.13 (0.01)
	p-value	--	--	0.008	0.011	--	--

Table 1: *Mean network measurements in AD and HC for each individual BN. Data are expressed as mean (SD). Note that MD and L1 weights are the most indicative. Eglob and mean nodal strength increased in AD for DMN and BGN.*

Results: rs-fMRI analysis showed that anterior insular (AIN), basal ganglia (BGN), cerebellum (CBLN) and DMN were the RSNs most involved by the pathology. DMN was divided in two RSNs: the first was functionally increased in AD (DMN) while the second was functionally reduced in AD (DMNr). CBLN consisted only of one cluster so it wasn't included in the BN analysis. To highlight the organization of each selected BN, Figure 1 shows all BN weighted using mean MD in HC and AD in the three radiological sections. No differences were found between AD and MCI and between MCI and HC. Table 1 reports the most significant BN results. *Eglob* and *mean nodal strength* increased significantly in AD when using MD and L1 as weights, while *local efficiency* showed no differences. DMN was the most involved, while BGN showed less significance and AIN showed no significances.

Discussion and conclusions: This work attempts to investigate the structural connectivity in spatially independent RSNs in AD and MCI with respect to HC. To the best of our knowledge, to date no study has focused on this issue; hence we tested brain connectivity by using different kind of diffusion proprieties as BNs weights in order to identify the best pathological marker but we couldn't reconstruct complex brain structures, such as crossing fibres connecting cerebellar and cerebral cortices, because DTI scan had 15 directions only. Since MD, L1 and RD increase in pathological conditions, an increment in *Eglob* when using these measurements as weights represents an increased pathological involvement rather than an effective increment of BN efficiency. Our findings reveal that FA weight is not useful to assess the entity of the alterations, while MD, L1 and RD are indicative of the pathological degree of alterations. MD and L1 are the best markers when used for calculating graph theory measurements, such as *Eglob* and *nodal strength*, as these identified alterations in two BNs (BGN and DMN) of AD. It is worth noticing that these measurements increased in AD in areas where functional connectivity both decreases (e.g. DMNr) and increases (e.g. DMN). Our findings suggest that it is essential to assess both functional and structural connectivity of RSNs to understand different stages of pathology, their alterations and possible evolution. Further studies combining advanced tractography and larger networks involving multiple RSNs, e.g. the cerebellum, are warranted to investigate whether they reveal alterations, possibly indicative of the presence of structural pathology affecting connectivity even at the earlier stage of the disease.

Acknowledgments: *We thank C. Mondino National Neurological Institute of Pavia (5 per mille 2011) and University of Pavia for funding.* **References:** *1. Binnewijzend MA et al. Neurobiol Aging (2012) 33:2018-2028; 2. Xiang J et al. Neural Regen Res (2013) 8(30):2789-2799; 3. Supekar K et al. NeuroImage (2010) 52:290-301; 4. Castellazzi G et al. Front Neurosci (2014) 8:1-18; 5. FMRIB Software, http://www.fmrib.ox.ac.uk/fsl/; 6. Rubinov M, Sporns O, NeuroImage (2010) 52(3):1059-1069.*