Multi-modal Analysis of Cortico-cortical Connectivity based on GM and WM Anatomical Properties: Application to Secondary Progressive Multiple Sclerosis

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Lobe	Cortical gyri included in the first PN
Frontal	**Superior Frontal**
	Rostral/Caudal **Middle Frontal**
	Pars Opercularis/Triangularis/Orbitalis**
	Lateral/Medial **Orbitofrontal**
	Precentral
	Paracentral**
	Rostral/Caudal* **Anterior Cingulate**
Parietal	Superior/**Inferior Parietal**
	Supramarginal
	Postcentral
	Precuneus
	Posterior Cingulate
Temporal	Superior/Middle/Inferior/Transverse* Temporal
	Fusiform
	Parahippocampal**
Occipital	Lateral Occipital
	Lingual
	Cuneus**

Table 1 *Regions in the first PN. */** detected only in the left/right hemisphere. In bold the subset for the WMDN.*

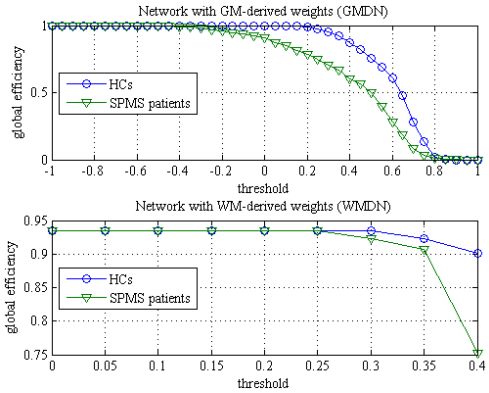

Figure 1 *Global efficiency of GMDN (top) and WMDN (bottom) of HC and patients for increasing data-driven thresholding values of connections weights. The two WMDN, having only 14 nodes, for thresholds > 0.4 became inconsistent.*

Cortical region	abs(Thk(HC) – Thk(SPMS)) /Thk(HC)x100
paracentral gyrus LH	4.96%
superior frontal gyrus RH	5.99%
precentral gyrus LH	7.02%
superior temporal gyrus RH	7.44%
lingual gyrus LH	9.40%
transverse temporal gyrus LH	9.97%
lingual gyrus RH	10.96%
transverse temporal gyrus RH	11.94%
pericalcarine cortex LH	12.32%
pericalcarine cortex RH	14.65%

Table 2 *Mann-Whitney U test results. Thk(group) = mean thickness in the group. LH/RH = Left/Right Hemisphere. In the box: regions with the highest difference values were detected in both LH and RH.*

Quantile	GM-derived weights	WM-derived weights
0%	0.29	0
25%	0.51	0.42
50%	0.56	0.44
75%	0.66	0.47
100%	1	0.57

Table 3 *Example of different distributions of the quantiles for GM-derived and WM-derived weighting values of edges incident to a same region (fusiform gyrus RH).*

TARGET AUDIENCE: Scientists and physicians interested in studying brain connectivity from quantitative properties of grey matter (GM) and white matter (WM), and in evaluating connectivity modifications in Multiple Sclerosis (MS).

INTRODUCTION AND PURPOSE: Cortico-cortical networks can be described by graphs in which nodes represent regions of the brain cortex and links show their anatomical, functional or effective relationships. Evolution of the cortex is thought to reflect the subdivisions underpinning brain function[1]; so, between-subject correlation of cortical thickness can be regarded as a GM-derived measure of connectivity. Thickness-based similarity of two regions might stem from their anatomical connection through the WM substrates[2]; based on this, also a measure of diffusivity in the fibres, e. g. fractional anisotropy (FA), can be regarded as a WM-derived measure of connectivity. In this work we identify a relevant set of cortical regions and we develop a multi-modal weighting approach for their interconnections, determining a "GM-derived network" (GMDN) and a "WM-derived network" (WMDN). We then investigate the properties of GMDN and WMDN determined from data of two groups: healthy controls (HC) and patients with Secondary Progressive Multiple Sclerosis (SPMS). We finally test if GMDN and WMDN provide the same information about connectivity.

METHODS: Subjects: 32 HC and 13 SPMS patients; a previous study[3] implemented a scoring system and selected these subjects in which performance of FreeSurfer cortical reconstruction process was excellent. Images acquisition: images were acquired on a 3T Philips Achieva MRI scanner with a 32-channel head coil. All participants gave written informed consent. All subjects underwent a 3D sagittal T1-w FFE scan (1x1x1 mm^3 voxel size, TR/TE = 6.9/3.1 ms). 31 HC and all patients also underwent: 1) a cardiac-gated SE-EPI HARDI (2x2x2 mm^3 voxel size, 61 isotropically distributed diffusion-weighted (DW) directions [b = 1200 s/mm^2], 7 non-DW volumes [b = 0], TR = 24 s (depending on cardiac rate), TE = 68 ms, SENSE factor = 3.1); 2) a dual-echo proton density/T2-w (1x1x3 mm^3 voxel size, TR = 3500 ms, TE = 19/85 ms). 1) and 2) were acquired axial-oblique and aligned with the anterior-posterior commissure. GM-derived weights: each subject's cortical thickness was measured in 64 areas (FreeSurfer, Desikan-Killiany atlas). At a macro-scale human brain networks have a "small-world" organisation[4], hence connectivity must be investigated in highly-interconnected subnetworks: we considered the cortical regions included in the "first Principal Network" (first PN), which is the main brain subnetwork of HC calculated from between-HC correlations of cortical thickness[5]. The first PN was considered as the GMDN for HC, while the GMDN for SPMS patients was obtained by substitution of first PN's weights with between-patients correlations of cortical thickness rather than recalculating it. Cortical regions selection: to reduce computational times, only first PN's highly interconnected regions (GM-derived weights for HC $\geq$ 0.5) and their counterparts in the other hemisphere were considered to form the two WMDN**.** Diffusion analysis: following steps involved only subjects with all MRI scans. HARDI images were processed with a previously presented pipeline[6]. Probabilistic tractography (MRtrix) was run for HC between each pair of selected cortical regions (tracks no. = 200000). Diffusion tensor components and maps of FA were also created for all the subjects (MRtrix). Tracts masks: using FSL, a mean mask of each tract was generated in the International Consortium for Brain Mapping (ICBM) atlas. All tracts were normalised to that atlas (NiftyReg, previously presented pipeline[7]), thresholded to 20% and binarized. A mean tract was generated for each pair of selected cortical regions, thresholded to 70% and binarized to obtain the corresponding mask. WM-derived weights: tracts masks were applied to all maps of FA. Mean FA was computed in the two groups for all tracts and used to weight the cortico-cortical links in the corresponding WMDN. Networks comparison: HC versus SPMS patients comparison of GMDN and WMDN was performed by applying a data-driven range of equally spaced thresholds (step = 0.05) to the connection weights of the network and by calculating the corresponding values of global efficiency. Thresholds were chosen to span the ranges of correlation and FA values, which are [-1, 1] and [0, 1], respectively. To determine which regions were statistically different in the two groups based either on their GM-derived or on their WM-derived weights, two non-parametric Mann-Whitney U test were performed (R software; test parameters: global confidence level = 0.95, Bonferroni's correction). Finally, focusing on GMDN and WMDN of HC, the distributions of GM-based and WM-based weights for links incident common vertices were compared through their quantiles.

RESULTS: The first PN comprised 48 fully-connected cortical regions (Table 1), of which 7 were highly-interconnected (Table 1, bold). As a function of the weights threshold, figure 1 shows that global efficiency was systematically lower in connectivity networks of SPMS patients versus HC. As a result of the Mann-Whitney U test for the cortical thickness distributions, Table 1 shows thickness-based statistical difference between the two groups of 10/48 regions. As a result of the Mann-Whitney U test for the FA distributions, all WM tracts were statistically different between the two groups. Finally, for each cortical region common to GMDN and WMDN of HC, the distributions of GM-derived and WM-derived weights had different quantiles. As a representative example, Table 3 shows the quantiles determined for the fusiform gyrus in the right hemisphere.

DISCUSSION AND CONCLUSION: We developed a method to analyse connectivity between relevant sets of brain cortical regions: we chose them according to the PNs analysis and we weighted their connections with quantitative MRI measures derived from GM and WM anatomical properties. We showed that a disease-related connectivity impairment was detectable with both the weighting modalities, so we propose GMDN and WMDN as tools for monitoring changes of connectivity properties in MS. However, we highlight the importance of interpreting GMDN and WMDN information in a complementary way, since their weights resulted to be statistically uncorrelated.

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