MULTI-MODAL ANALYSIS OF CORTICO-CORTICAL CONNECTIVITY BASED ON GM AND WM ANATOMICAL PROPERTIES: APPLICATION TO SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

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Target audience: Scientists and physicians interested in studying brain connectivity using quantitative measures of grey matter (GM) and white matter (WM) tissues, and in particular the use of such techniques to assess the impairment of brain connectivity due to WM and GM pathology in people with multiple sclerosis (MS)[1].

Introduction: Cortico-cortical networks can be described by graphs, in which nodes represent regions of the brain cortex and edges show their anatomical, functional or effective relationships. The structural development of the cortex is thought to reflect its functional subdivisions[2], so between-subject correlation of cortical thickness can be regarded as a GM-derived measure of connectivity[3]. However, similarity of two regions may also stem from connections via WM tracts[4]. Based on this, measure of diffusion anisotropy in WM fibres, such as fractional anisotropy (FA), may be regarded as a metric of the strength of a connection between regions. In this work we identify a set of functionally relevant 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.

Lobe	Cortical gyri included in the first PN
Frontal	Superior Frontal, Caudal/Rostral Middle Frontal, Pars Opercularis/Triangularis/Orbitalis** Medial/Lateral Orbitofrontal, Precentral, Paracentral**, Caudal*/ Rostral 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. The subset for the WMDN is underlined.*

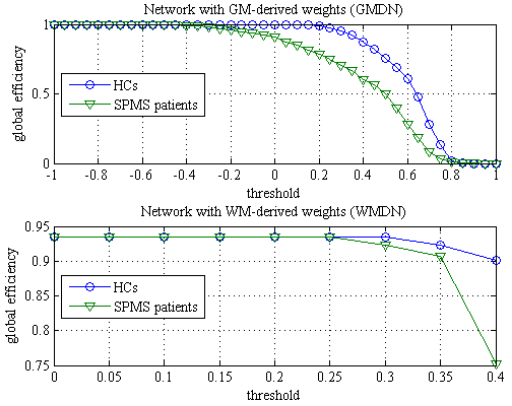

Figure 1 *Global efficiency of GMDN (top) and WMDN (bottom) of HC and patients for increasing data-driven thresholding values of connection weights. WMDN had 14 nodes, which were found to be disconnected for weight thresholds > 0.4.*

Cortical gyrus	abs(Thk(HC) – Thk(SPMS)) /Thk(HC)x100
paracentral LH	4.96%
superior frontal RH	5.99%
precentral LH	7.02%
superior temporal RH	7.44%
lingual LH	9.40%
transverse temporal LH	9.97%
lingual RH	10.96%
transverse temporal 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.*

Cortical gyrus	Rho LH/RH	P-value LH/RH
Fusiform	-0.02/-0.00	0.93/0.99
Inferior parietal	0.02/0.06	0.95/0.83
Lateral orbitofrontal	0.26/0.11	0.36/0.71
Posterior cingulate	-0.03/-0.29	0.93/0.31
Precuneus	-0.14/-0.03	0.63/0.91
Rostral anterior cingulate	-0.35/-0.24	0.23/0.41
Superior frontal	-0.56/-0.18	0.04/0.53

Table 3 *Results of Spearman's correlation test for GM/WM-derived weights of edges incident to the same cortical region.*

Methods: Subjects: 32 HC (16F and 16M, mean age 39 ± 13 yrs) and 13 people with SPMS (9F and 4M, mean age 57 ± 6 yrs); a previous study[5] implemented a scoring system and selected these subjects in which performance of FreeSurfer cortical reconstruction process was excellent. Image 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 the whole MS group 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[6], hence it is reasonable to investigate connectivity 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[7]. 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-patient correlations of cortical thickness rather than recalculating it. Cortical region selection: To reduce computation time, 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: HARDI images were pre-processed with a previously presented pipeline[8]. 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). Tract masks: A mean mask of each tract was generated in the International Consortium for Brain Mapping (ICBM) atlas (FSL). Probabilistic maps resulting from tractography analysis were registered to the atlas (NiftyReg, previously presented pipeline[9]), individual tracts were thresholded to 20% and binarized to obtain single-tract masks. A mean map of each tract was then generated by summing analogous single-tract masks, thresholding them to 70% and binarizing the thresholded output. WM-derived weights: Mean FA was computed in the two groups for all the tracts and used to weight the cortico-cortical links in the corresponding WMDN. Network 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[6]. 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 tests were performed (R software; test parameters: global confidence level = 0.95, Bonferroni's correction). Finally, focusing on GMDN and WMDN of HC, Spearman's correlation of GM-based and WM-based weights for links incident common vertices was determined.

Results: The first PN comprised 48 fully-connected cortical regions (Table 1), that is, every region was connected to every other; 14 regions (Table 1, underlined) were highly-interconnected. As a function of the weight threshold, global efficiency was systematically lower in connectivity networks of SPMS patients versus HC (Figure 1). There was thickness-based statistical difference of 10/48 regions between the two groups (Table 2), while FA-based statistical difference between the two groups was found for all WM tracts. Finally, for each cortical region common to GMDN and WMDN of HC, GM/WM-derived weights were found to be statistically uncorrelated (Table 3).

Discussion and conclusion: We developed a method to analyse connectivity between relevant sets of cortical regions, chosen according to the PNs analysis. We weighted their connections with quantitative MRI measures derived from GM and WM anatomical properties. We found that in HC GMDN and WMDN did not correlate, suggesting that they provide at least partly independent information about networks, and that a disease-related connectivity impairment was detectable with both the weighting modalities. Given this, GMDN and WMDN may have a complimentary role monitoring changes in the connectivity properties of brain networks in MS.

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