Title
Predictive modelling of multiple sclerosis based on whole-brain functional connectivity

Authors
Jonas Richiardi[a,b], Markus Gschwind[a,d], Samanta Simioni[e], Jean-Marie Annoni[a,d], Beatrice Greco[c], Patric Hagmann[c,e], Myriam Schluep[e], Patrik Vuilleumier[a,d], Dimitri Van De Ville[a,b]

a University of Geneva, Switzerland
b Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland
c Merck-Serono, Geneva, Switzerland
d University Hospital Geneva (HUG), Switzerland
e University Hospital Lausanne (CHUV), Switzerland

Introduction
Early treatment in Multiple Sclerosis (MS) is crucial to avoid damage and to delay disease progression. However, early identification of the disease is problematic, and structural MRI has several limitations; e.g., the "hidden" damage known to occur in the normal appearing brain tissue (NABT) is not revealed. There may be potential gains from using other MRI contrasts in MS. Here, we explore the potential of fMRI functional connectivity at rest to serve as a prospective imaging marker of the disease.

Methods
Subjects
22 relapsing-remitting MS patients were recruited, with: (1) mild to moderate neurological disability but unimpaired ambulation (Expanded Disability Status Scale (EDSS) ≤ 2.5 (Kurtzke, 1983)); (2) no clinical relapse and no corticosteroid therapy for at least 6 weeks before inclusion; (3) no other neurological or psychological diagnosis.

Data acquisition
Data was acquired on a Siemens 3T Trio, with a 32-channel head coil. fMRI data were acquired in one session using GRE-EPI (TR/TE/FA = 1.1s/27ms/90◦, matrix = 64×64, voxel size = 3.75×3.75×5.63mm3, 21 contiguous transverse slices, 450 volumes, around 8 minutes). The first 10 scans of each acquisition were discarded, yielding T = 440 volumes for analysis. Participants were instructed to lie still with their eyes closed.
A structural image was also acquired (3D T1-weighted MPRAGE sequence, 160 slices, TR/TE/FA = 2.4s/ 2.98ms/9◦, matrix = 256 × 240, voxel size = 1 × 1 × 1.2mm3).

Data processing and construction of the functional connectivity matrix
As in Achard et al., 2006; and Richiardi et al., 2011, the functional data is realigned, coregistered with the structural data, and a functional atlas is computed by inverse-warping an individual 90-regions AAL atlas (Tzourio-Mazoyer et al. 2002) obtained on structural data. The functional data in each region is averaged, and these regional averages are wavelet-filtered into the

0.06–0.11 Hz band. The filtered regional timecourses are correlated pairwise; yielding a functional connectivity matrix **C**. No thresholding is applied.

Modelling and classification of connectivity matrices
The matrix **A**=**C**-diag(diag(**C**)) is a valid adjacency matrix for an undirected weighted graph. We use the direct graph embedding method (Richiardi et al., 2010): the upper-triangular part of **A** is lexicographically organized in a high-dimensional vector. An ensemble classifier (21 functional trees, see Richiardi et al., 2011) is used to learn and apply a discriminative function on each subject's vector in a leave-one-subject-out cross-validation scheme.

Results

Sensitivity and Specificity
18 out of 22 patients and 12 out of 14 controls were classified correctly; corresponding to a sensitivity of 82% (above chance at $p < 0.005$), and a specificity of 86% ($p < 0.01$). Patient treatment had no effect on classification performance.

Discriminative network topology
Only 161 connections out the full 4005 have significant discriminative weights ($p<0.05$, corrected for multiple comparisons by permutation testing) for patients versus controls (Figure 1). The overall pattern of changes reveals a network of functional connections mainly centred on subcortical and fronto-parieto-temporal regions, consistent with the typically widely distributed lesions in MS.

Discriminative connections are predominately inter-lobe, but intra-lobe connections are equally or more important for temporo-parietal regions (Figure 2). They correspond to long-range pathways in the posterior-anterior axis along the periventricular regions. Connections to and from subcortical regions are also particularly discriminative, hinting at the widespread connectivity of these structures.

Conclusions

Our results confirm that functional changes affecting cortical and subcortical networks are a prominent feature of MS brain pathology, but also show that these alterations can be sensitively measured using functional MRI of resting state, and furthermore be used to classify disease state in individual subjects.

Figures

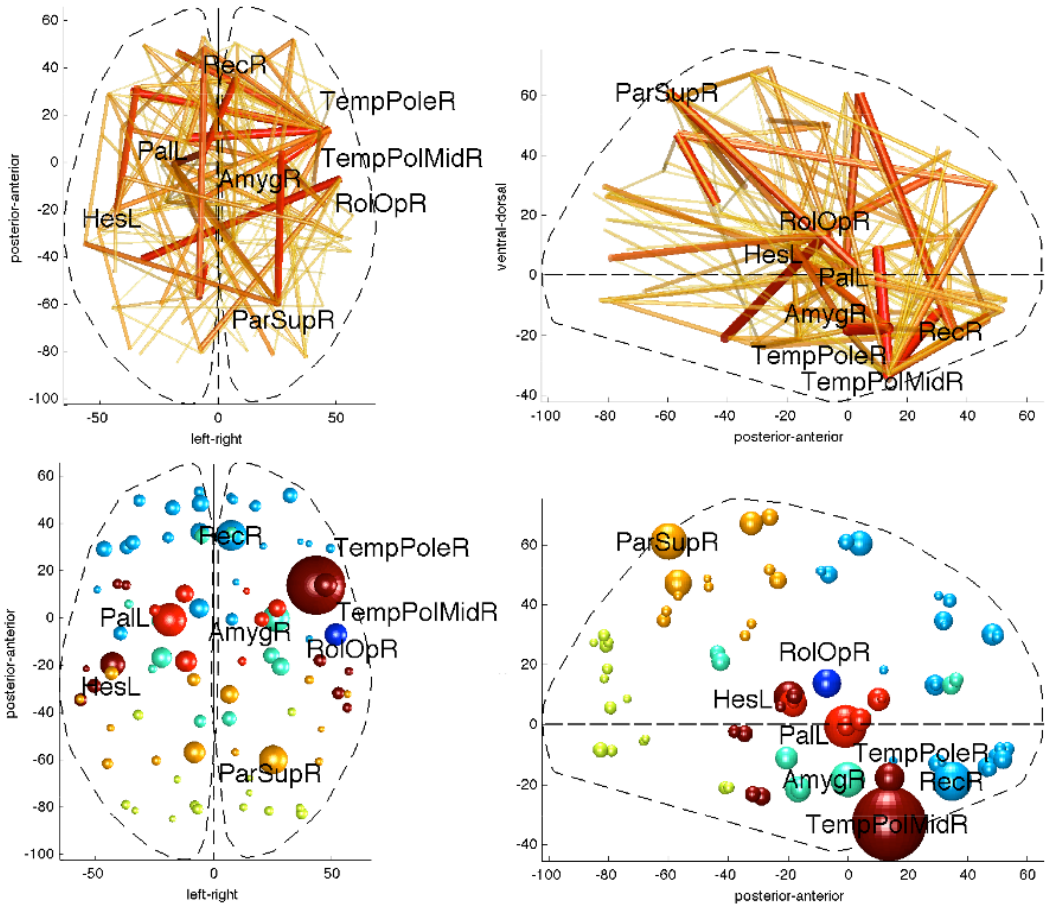

Figure 1: Anatomical illustration of discriminative graphs for MS versus control subjects. In the top row, the size and shade of connections between regions reflects their relative discriminative weight: stronger hues and larger sizes reflect higher discriminative weight. In the bottom row, the size of each sphere depicting an atlas region is proportional to its regional discriminative weight (sum of the discriminative weights of all connections between this region and the rest of the brain). Colour indicates the lobe where each region is located (dark red = temporal, clear blue = frontal, yellow = parietal, green = occipital, cyan = limbic structures (cingulum, hippocampus and parahippocampal formation, amygdala) and insula, clear red = subcortical grey matter). Name labels are given for the region, with the highest regional discriminative weights (limited to 8 for clarity). Note that this a multivariate pattern and individual connections are not discriminative on their own.

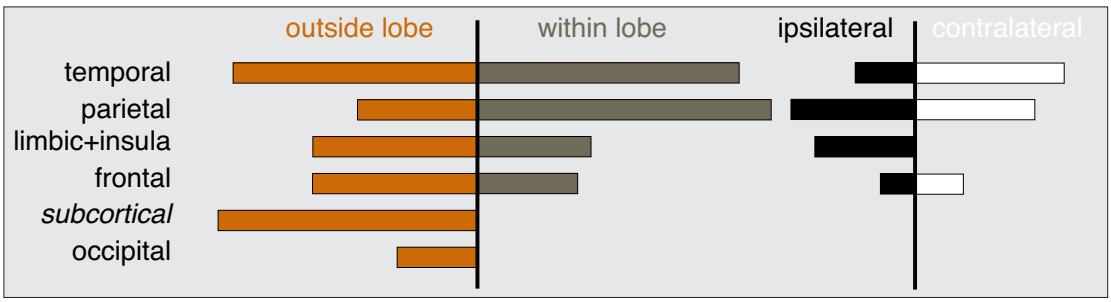

Figure 2: (left graph) Summary of discriminative weights of ROIs by lobe, distinguishing connections that link to other regions outside the lobe from connections that stay within the same lobe. The lobes are ordered from overall most discriminative to overall least discriminative. Limbic structures include cingulum, hippocampus and parahippocampal formation, and amygdala. (right graph) Further subdivision of within-lobe connections into ipsilateral and contralateral connections.

References

Achard, S., Salvador, R., Whitcher, B., Suckling, J., Bullmore, E., Jan. 2006. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. The Journal of Neuroscience 26 (1), 63–72.

Barkhof, F., Filippi, M., Apr. 2009. Multiple sclerosis: MRI–the perfect surrogate marker for multiple sclerosis? Nature Reviews Neurology 5 (4), 182-183.

Kurtzke, J. F., Nov 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33 (11), 1444–1452.

Richiardi, J., Van De Ville, D., Riesen, K., Bunke, H., 2010. Vector space embedding of undirected graphs with fixed-cardinality vertex sequences for classification. In: Proc. 20th Int. Conf. on Pattern Recognition (ICPR). pp. 902–905.

Richiardi, J., Eryilmaz, H., Schwartz, S., Vuilleumier, P., Van De Ville, D., May 2011. Decoding brain states from fMRI connectivity graphs. NeuroImage (Special Issue on Multivariate Decoding and Brain Reading) 56 (2), 616–626

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O.,Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289