Recovery from an acute relapse is associated with changes in motor resting-state connectivity in multiple sclerosis

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INTRODUCTION

Resting-state functional MRI (rs-fMRI) of the brain has been successfully used to identify altered functional connectivity in the motor network in multiple sclerosis (MS). In clinically stable patients with MS, we recently demonstrated increased coupling between the basal ganglia and the motor network. Accordingly, rs-fMRI in MS is particularly suited to investigate functional reorganisation of the motor network in the remission phase after a relapse because the resting-state connectivity pattern is not influenced by interindividual differences in motor ability and task performance. In this prospective rs-fMRI study, we mapped acute changes in resting-state motor connectivity in 12 patients with relapsing forms of MS presenting with an acute relapse involving an upper limb paresis. Previous functional MRI (fMRI) studies have shown that the activation of sensorimotor areas was stronger and more widespread in the brain of patients with MS compared to healthy controls and increased proportionally with the extent of MS-related brain damage. We therefore hypothesised that a motor relapse involving paresis of the upper limbs would trigger an acute compensatory increase in motor resting-state connectivity and that the compensatory increase in functional connectivity would decrease over the following days or weeks in proportion to the degree of clinical remission.

SUBJECTS AND METHODS

Participants

We studied 12 patients with MS presenting with acute motor deficits involving paresis of the left (n=5) or right (n=7) arm. MRI and neurological examination including Expanded Disability Status Scale (EDSS) score was performed twice, at inclusion and at follow-up. The relapse was treated with a three-day course of intravenous methylprednisolone 1 g daily which was initiated after the first scan. Written informed consent was obtained from all patients prior to any examination, and all protocols were approved by the local scientific ethical committee (protocol no. KF01–131/03). Clinical characteristics are listed in table 1 (see online supplementary material).

MRI

MRI was performed on a Siemens 3.0 T Magnetom Trio Scanner using echo planar imaging. The first rs-fMRI was performed within 24 h after relapse onset, while the second rs-fMRI was obtained 6 to 21 days later. Please refer to online supplementary material for further details.

Resting-state connectivity analysis

Independent component analysis (ICA) was applied to the fMRI data to separate functional brain networks that show temporally correlated BOLD-signal fluctuations. We performed spatial ICA using the Group-ICA-Toolbox for fMRI (http://icatb.sourceforge.net/) with the number of
components fixed at 20. The sensorimotor network and two control networks, the primary visual and the default-mode network, were identified by a template matching procedure. Details are provided in online supplementary material.

**Statistical analysis**

We aimed at capturing changes in motor resting-state connectivity between onset of the motor relapse and after a remission period of 6–21 days, (ie, between the first and second rs-fMRI session). Specifically, we wished to test which brain regions that showed a reduction in motor resting-state connectivity in proportion to clinical remission by assessing changes in motor resting-state connectivity during the acute remission phase relative to the acute relapse phase. We found that the SMA and mesial M1 reduced its connectivity strength with the network. No brain regions showed the opposite relationship, an increase in motor resting-state connectivity with increasing motor remission. No significant change in motor resting-state connectivity was detected over time. The four axial slices are arranged from most caudal to most cranial (z-coordinates, Montreal Neurological Institute (MNI)) and the three coronal slices are arranged from most posterior to most anterior (y-coordinates, MNI). The red overlay indicates $t_{10}$ statistical values as shown in the colour bar to the right.

**RESULTS**

Regression analysis revealed a statistically significant relationship between improvement in EDSS score and reduction in motor resting-state connectivity in the supplementary motor area (SMA) and mesial primary motor cortex (M1) (figure 1; $p_{FWE}=0.002; t_{10}=7.58$; peak at Montreal Neurological Institute coordinates $x$, $y$, $z=-6, -25, 70$) while no brain regions showed the opposite relationship. Further, changes in EDSS score did not correlate with changes in resting-state connectivity in the primary visual or default-mode network.

**DISCUSSION**

We aimed at capturing changes in motor resting-state connectivity during the acute remission phase relative to the acute relapse phase. We found that the SMA and mesial M1 reduced its connectivity strength with the network. No brain regions showed the opposite relationship, an increase in motor resting-state connectivity with increasing motor remission. No significant change in motor resting-state connectivity was detected over time. The four axial slices are arranged from most caudal to most cranial (z-coordinates, Montreal Neurological Institute (MNI)) and the three coronal slices are arranged from most posterior to most anterior (y-coordinates, MNI). The red overlay indicates $t_{10}$ statistical values as shown in the colour bar to the right.

EDSS is strongly weighted towards motor function and in this study we used changes in EDSS score as a surrogate measure of clinical motor recovery. It would have been interesting to also include more direct and objective measures of motor performance such as the timed Nine-hole Peg Test and 25 feet Walk test. This would allow us to more specifically relate the dynamic changes in motor resting-state connectivity associated with a motor relapse to dexterity or walking. Another limitation of this study is the relative small random size and the fact that no rs-fMRI data was obtained before the relapse which would have required a large-scale prospective cohort study.

In summary, this prospective rs-fMRI study identified changes in resting-state functional connectivity in key motor regions in the acute phase of a MS relapse with paresis of an upper limb. Clinical improvement was associated with a weakening of motor resting-state connectivity in SMA extending into mesial M1, presumably indicating a normalisation of the connectivity pattern with recovery of motor function. It is possible that rs-fMRI may be able to distinguish between patients with MS with a favourable and poor motor outcome after an acute relapse based on the reorganisation pattern.
However, the potential of rs-fMRI to predict the individual capacity of spontaneous functional recovery requires studies that contrast the resting-state connectivity pattern in patients with a favourable and poor motor outcome after a relapse in a larger cohort of patients.

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Contributors A-MD contributed to the design of the study, recruitment of subjects, scanning and clinical evaluation of subjects, data analysis, interpretation of results and wrote the paper. MB contributed to the design of the study, recruitment of subjects, and commented on the paper. PSS contributed to the design of the study and commented on the paper. HRS contributed to the data analysis, interpretation of results and writing of the paper. KHM contributed to the design of the study, performed the analysis of imaging data, statistical analysis, interpretation of results and wrote the paper.

Competing interests MB reports serving on scientific advisory boards for Biogen Idec, Merck-Serono, Novartis, Sanofi-Aventis and Teva; receiving speaker honoraria from Biogen Idec, Merck-Serono, Bayer-Schering, Novartis, Teva and Sanofi-Aventis; has received consulting honoraria from the Danish Multiple Sclerosis Society, Biogen Idec and Merck-Serono; has received funding for travel from Biogen Idec, Merck-Serono, Sanofi-Aventis, Genzyme and Solvay Pharma. FS has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Bayer Schering, Biogen Idec, Genzyme, Lundbeck, Merck Serono, Novo Nordisk, Novartis, Sanofi-Aventis, Schering Plough and Teva. PSS reports having served on scientific advisory boards Biogen Idec, Merck Serono, Novartis, Gennab, TEVA, Elan, GSK; has been on steering committees or independent data monitoring boards in clinical trials sponsored by Merck Serono, Gennab, TEVA, GSK, Bayer Schering, and he has received funding of travel for these activities; has received speaker honoraria from Biogen Idec, Merck Serono, TEVA, Bayer Schering, Sanofi-Aventis, Genzyme and Novartis. HRS has received honoraria as speaker from Lundbeck A/S, Valby, Denmark, Biogen Idec, Denmark A/S, Genzyme, Denmark and MerckSerono, Amsterdam, the Netherlands and Springer Publishing, Stuttgart, Germany, travel support from MagVenture, Denmark and grant support from Biogen Idec, Denmark A/S.

Ethics approval Scientific ethics committee of Copenhagen and Frederiksberg Communities (protocol no. KF01—13I/03 with addendum).

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