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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).¹ In clinically stable patients with MS, we recently demonstrated increased coupling between the basal ganglia and the motor network.¹ 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.² 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.³ 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

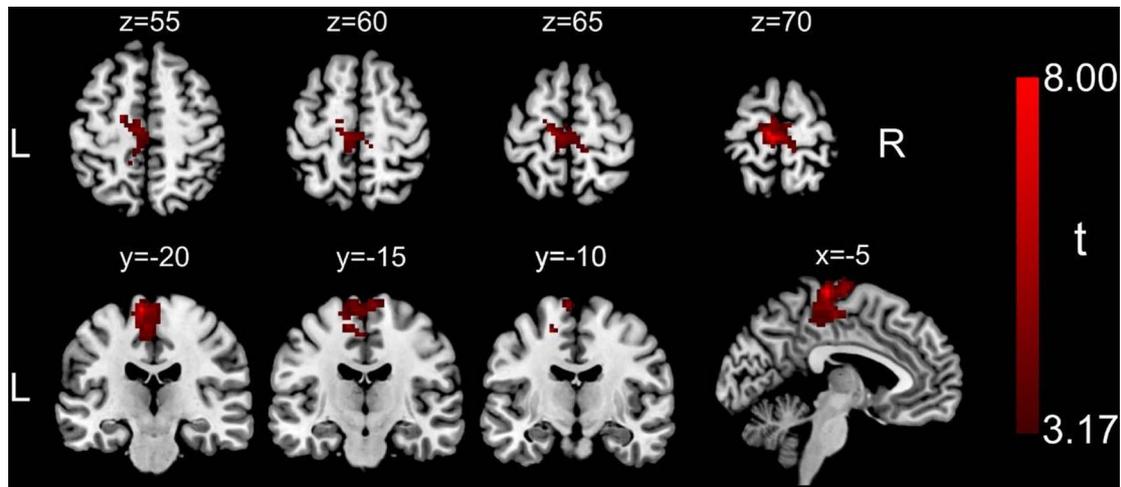


Figure 1 Changes in motor resting-state connectivity during the acute remission phase reflect clinical improvement. The supplementary motor area (SMA) and mesial primary motor cortex (M1) expressed a decrease in coupling strength with the motor resting-state network from the first to second fMRI session which reflected the magnitude of clinical improvement. The stronger motor remission, the more the SMA and mesial M1 reduced its functional 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.

components fixed at 20. The sensori-motor network and two control networks, the primary visual and the default-mode network, were identified by a template matching procedure.¹ 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 (time 2—time 1) with improvement in EDSS score as a covariate (time 2—time 1). The same analysis was performed for two non-motor networks, the primary visual and default-mode network. Correction for multiple comparison was performed using cluster-wise maximum permutation statistics with a two-sided entry threshold of $p < 0.01$. Clusters surviving a threshold of $p_{FWE} < 0.05$ corrected for multiple comparisons over the whole brain were considered statistically significant.

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) extending into the bilateral 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 found that the SMA and mesial M1 reduced its connectivity strength with the motor network in proportion to recovery of motor function after acute relapse. The SMA and M1 are key motor regions. SMA integrates converging input from subcortical motor (basal ganglia, thalamus and cerebellum) and parietal cortex afferents, and sends projections to the M1 and directly to the corticospinal tract.⁴ An acute relapse might therefore trigger a compensatory increase in functional resting-state motor connectivity involving the SMA. Our results indirectly support this notion, showing that the strength in motor resting-state connectivity of SMA decrease in proportion to functional recovery of motor function. The reduced coupling of SMA and M1 to the motor network most likely reflects a return to a normal pattern of resting-state motor connectivity paralleling clinical motor improvement.

Neither the visual nor the default-mode network showed regional connectivity changes scaled to the magnitude of motor recovery, suggesting that the reorganisation associated with the acute motor lesion was spatially specific to the motor network. The network-specific pattern of

functional reorganisation is reminiscent to a recent rs-fMRI study in a stroke cohort with heterogeneous acute stroke lesions. In that study, changes in functional brain connectivity during recovery were mainly restricted to networks that contained the focal stroke lesion.⁵

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.³ 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 sample 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.

Anne-Marie Dogonowski,¹ Morten Blinkenberg,² Olaf B Paulson,^{1,3} Finn Sellebjerg,² Per Soelberg Sørensen,² Hartwig R Siebner,^{1,4} Kristoffer H Madsen^{1,5}

¹Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital, Hvidovre, Denmark

²Danish Multiple Sclerosis Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

³Neurobiology Research Unit, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

⁴Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark

⁵Cognitive Systems, Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kgs. Lyngby, Denmark

Correspondence to Dr Anne-Marie Dogonowski, Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Hvidovre 2650, Denmark; amdogonowski@hotmail.com

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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, discussed the results and commented on the paper. OBP contributed to the design of the study and commented on the paper. FS 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, Genmab, TEVA, Elan, GSK; has been on steering committees or independent data monitoring boards in clinical trials sponsored by Merck Serono, Genmab, 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, Denmark, honoraria as editor from Elsevier Publishers, 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—131/03 with addendum).

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