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Multiple sclerosis impairs regional functional connectivity in the cerebellum ☆

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ABSTRACT

Resting-state functional magnetic resonance imaging (rs-fMRI) has been used to study changes in long-range functional brain connectivity in multiple sclerosis (MS). Yet little is known about how MS affects functional brain connectivity at the local level. Here we studied 42 patients with MS and 30 matched healthy controls with whole-brain rs-fMRI at 3 T to examine local functional connectivity. Using the Kendall's Coefficient of Concordance, regional homogeneity of blood-oxygen-level-dependent (BOLD)-signal fluctuations was calculated for each voxel and used as a measure of local connectivity. Patients with MS showed a decrease in regional homogeneity in the upper left cerebellar hemisphere in lobules V and VI relative to healthy controls. Similar trend changes in regional homogeneity were present in the right cerebellar hemisphere. The results indicate a disintegration of regional processing in the cerebellum in MS. This might be caused by a functional disruption of cortico-ponto-cerebellar and spino-cerebellar inputs, since patients with higher lesion load in the left cerebellar peduncles showed a stronger reduction in cerebellar homogeneity. In patients, two clusters in the left posterior cerebellum expressed a reduction in regional homogeneity with increasing global disability as reflected by the Expanded Disability Status Scale (EDSS) score or higher ataxia scores. The two clusters were mainly located in Crus I and extended into Crus II and the dentate nucleus but with little spatial overlap. These findings suggest a link between impaired regional integration in the cerebellum and general disability and ataxia.

1. Introduction

Multiple sclerosis (MS) is characterised by disseminated inflammatory demyelination and axonal degeneration in the central nervous system. The disease-related tissue damage delays and disrupts neural signal transmission along cortico-cortical and cortico-subcortical connections (Trapp et al., 1998), causing inefficient information transfer between brain regions. Accordingly, functional magnetic resonance imaging (fMRI) of spontaneous fluctuations in the blood-oxygen-level-dependent (BOLD)-signal during the resting-state has demonstrated changes in long-range functional connectivity of MS patients in the motor network (Dogonowski et al., 2012; Lowe et al., 2002; Roosendaal et al., 2010) and the default-mode network (Hawellek et al., 2011; Rocca et al., 2010).

In addition to studying long-range connectivity within functional brain networks, resting-state fMRI (rs-fMRI) can also be used to assess local connectivity in a brain region. The homogeneity of resting-state BOLD-signal fluctuations in neighbouring voxels reflects local brain connectivity (Zang et al., 2004). Regional homogeneity has successfully been used to identify abnormal local connectivity in pathological conditions such as neuromyelitis optica, Alzheimer's and Parkinson's disease (He et al., 2007; Liang et al., 2011; Wu et al., 2009). Here we employed regional homogeneity analysis of resting-state BOLD-signal fluctuations to test for brain regions where MS patients express an abnormal pattern of local functional connectivity relative to healthy controls. Within the patient group, we were also interested to identify brain regions where the regional expression of local resting-state connectivity would predict clinical disability.

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2. Subjects and methods

2.1. Patients and healthy subjects

Forty-two patients with definite MS fulfilling the revised McDonald criteria (Polman et al., 2005) and 30 sex- and age-matched healthy controls participated in the study. 39 of the 42 patients and 27 of the 30 healthy controls were right-handed as revealed by the Edinburgh Inventory (Table 1) (Oldfield, 1971). Healthy subjects had no history of neurological or psychiatric disease. The study was approved by the scientific ethics committee of Copenhagen and Frederiksberg Communities (protocol no. KF01—131/03 with addendum) and all subjects gave written informed consent.

Patients were recruited from The Danish Multiple Sclerosis Center, Copenhagen, Denmark and comprised 27 patients with relapsing–remitting MS (RR-MS) and 15 patients with secondary progressive MS (SP-MS) (Table 1). Only clinically stable patients who had not experienced a relapse in the three months preceding the magnetic resonance imaging (MRI) measurement were included. Neurological or psychiatric symptoms not attributable to MS were defined as exclusion criteria. Patients were neurologically examined and clinical disability was rated using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The EDSS score ranges from 0 to 10 where 0 equals a normal neurological examination and higher scores indicate more disability. In our patient group, EDSS scores ranged from 0–7 (median score: 4.3). The degree of ataxia was rated using the Multiple Sclerosis Impairment Scale (Ravnborg et al., 1997). The ataxia score evaluated upper and lower limb ataxia and ranges from 0 to 16, where 0 equals no ataxia and the highest scores correspond to the inability to perform coordinated movements. The individual ataxia scores ranged from 0–13 (median score: 3). 81% of the patients (n = 34) presented with ataxia defined as having an ataxia score above 0.

2.2. Magnetic resonance imaging

MRI measurements were performed on a 3 T Magnetom Trio scanner. All rs-fMRI measurements were recorded with a standard single-channel birdcage head-coil using a T2*-weighted echo planar imaging (EPI) sequence with a repetition time (TR) of 2490 ms, an echo time (TE) of 30 ms and a flip angle of 90°. In total 480 whole-brain volumes were acquired over 20 min. A brain volume consisted of 42 contiguous axial slices with a slice thickness of 3 mm and a 64 × 64 acquisition matrix covering a field of view = 192 × 192 mm. The resulting voxel size was 3 × 3 × 3 mm. Subjects were instructed to rest with their eyes closed without falling asleep, and refrain from any voluntary cognitive or motor activity. After the experiment, participants were asked whether they managed to stay awake. All participants reported that they did not fall asleep during scanning. The cardiac cycle was monitored with an infrared pulse oximeter attached to the index finger. Respiration was monitored with a pneumatic thoracic belt. Participants refrained from caffeine, cigarettes or alcohol intake six hours prior to the fMRI-session. Patients continued to take their usual medication.

Additionally, high-resolution three-dimensional structural MRI scans of the brain were acquired using an eight-channel phased array coil (Invivo, FL, USA). A sagittal magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequence (TR = 1550 ms, TE = 3.04, inversion time = 800 ms; flip-angle = 9°) was acquired consisting of 192 contiguous slices with a voxel size of 1 × 1 × 1 mm and an acquisition matrix of 256 × 256. In addition, sagittal turbo spin echo (TSE) images (TR = 3000 ms, TE = 354 ms) and fluid-attenuated inversion recovery (FLAIR) images (TR = 6000 ms, TE = 353 ms) were obtained. The TSE and FLAIR images covered the whole brain consisting of 192 slices with a voxel size of 1.1 × 1.1 × 1.1 mm and a 256 × 256 acquisition matrix. The structural scans were used to estimate total lesion load of cerebral white-matter in MS patients and to exclude subclinical white-matter lesions in healthy controls. Whole-brain lesion load was quantified using a semi-automatic lesion segmentation method guided by expert knowledge as described previously (Dogonowski et al., 2012).

Patients with MS showed reduced regional homogeneity in the cerebellum. This prompted us to perform a follow-up analysis on the patient data in which we tested for a linear relationship between lesion load in the cerebellar peduncles and the cortico-spinal tract (CST) and the change in regional homogeneity in the cerebellum. Lesion load in the cerebellar peduncles was estimated by extracting the cerebellar peduncles including the inferior, middle, and superior cerebellar peduncles as defined in the JHU white-matter tractography atlas and split into a left and right region-of-interest (ROI) (Hua et al., 2008). Lesion load of the inferior, middle, and superior cerebellar peduncles was also estimated individually. The ROI applied to estimate lesion load of the left, right and combined CST was specified as defined in JHU white-matter tractography atlas (Hua et al., 2008).

Table 1
Demographics and clinical characteristics.

	Healthy controls	Patients with MS	RR-MS	SP-MS
Number of subjects	30	42	27	15
(men; women)	(15; 15)	(20; 22)	(10; 17)	(10; 5)
Median age in years	45	45	39	51
(range)	(22–69)	(25–64)	(25–59)	(30–64)
Handedness	27; 2; 1	39; 3; 0	26; 1; 0	13; 2; 0
right; left; ambidextrous				
Median disease duration in years	n.a.	11.5	9	20
(range)		(3–43)	(3–27)	(6–43)
Median EDSS score	n.a.	4.3	3.5	6.0
(range)		(0–7)	(0–6.5)	(3.5–7.0)
Median ataxia score	n.a.	3.0	2.0	4.0
(range)		(0–13)	(0–13)	(1–10)
Median whole-brain lesion load in ml	n.a.	21.4 (n = 41)	17.4 (n = 26)	35.8 (n = 15)
(range)		(1.8–126.3)	(1.8–96.6)	(3.7–126.3)
Median lesion load in left and right cerebellar peduncles in ml	n.a.	0.04	0.05	0.04
(range)		(0–1.1)	(0–1.1)	(0–0.8)
Treatment	n.a.	35	24	11
IFN-β	n.a.	6	6	0
Glatiramer acetate	n.a.	9	9	0
Natalizumab	n.a.	5	5	0
Immunosuppresive agents	n.a.	10	5	5
Other	n.a.	6	0	6

MS = multiple sclerosis; RR-MS = relapsing–remitting multiple sclerosis; SP-MS = secondary progressive multiple sclerosis; n.a. = not applicable; EDSS = Expanded Disability Status Scale; IFN = Interferone.