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Altered thalamic functional connectivity in multiple sclerosis

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ABSTRACT

Objective: To compare thalamic functional connectivity (FC) in patients with multiple sclerosis (MS) and healthy controls (HC), and correlate these connectivity measures with other MRI and clinical variables.
Methods: We employed resting-state functional MRI (fMRI) to examine changes in thalamic connectivity by comparing thirty-five patients with MS and 35 age- and sex-matched HC. Thalamic FC was investigated by correlating low frequency fMRI signal fluctuations in thalamic voxels with voxels in all other brain regions. Additionally thalamic volume fraction (TF), T2 lesion volume (T2LV), EDSS and disease duration were recorded and correlated with the FC changes.
Results: MS patients were found to have a significantly lower TF than HC in bilateral thalami. Compared to HC, the MS group showed significantly decreased FC between thalamus and several brain regions including right middle frontal and parahippocampal gyri, and the left inferior parietal lobule. Increased intra- and inter-thalamic FC was observed in the MS group compared to HC. These FC alterations were not correlated with T2LV, thalamic volume or lesions. In the MS group, however, there was a negative correlation between disease duration and inter-thalamic connectivity ($r = -0.59$, $p < 0.001$).
Conclusion: We demonstrated decreased FC between thalamus and several cortical regions, while increased intra- and inter-thalamic connectivity in MS patients. These complex functional changes reflect impairments and/or adaptations that are independent of T2LV, thalamic volume or presence of thalamic lesions. The negative correlation between disease duration and inter-thalamic connectivity could indicate an adaptive role of thalamus that is gradually lost with increasing disease duration.

1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disorder of the central nervous system (CNS). It has been traditionally recognized as predominantly involving the white matter (WM). However, gray matter, including deep gray matter, damage is now known to be prevalent in MS. This gray matter injury, caused by widespread axonal and neuronal degeneration, is thought to contribute substantially to MS disability progression [1–3].

The thalamus, a key part of the deep gray matter, has extensive afferent and efferent connections with spinal afferents, the midbrain and the cerebral cortex. It is involved in motor planning, sensory information processing and many cognitive functions [4,5]. Numerous previous studies have demonstrated damage to the thalamus in MS, such as decreased neuronal integrity, loss of neurons and macroscopic atrophy [6], and MRI abnormalities including T2 hypointensity [7], hypometabolism [8], decreased NAA [9] and increased diffusivity [10]. Furthermore, in several task-specific functional MRI studies, abnormal activation of the thalamus had been widely reported in patients with CIS and MS [11–15].

Resting-state fMRI, as a relatively new branch of functional imaging, reflects baseline neural network connectivity in the "unattended" state, and assesses between-voxel correlations in spontaneous blood oxygen level dependent (BOLD) fluctuations. Functional connectivity (FC) changes in MS have been observed by resting-state fMRI in brain network or regions such as brain default mode network (DMN), the motor network, the hippocampus and the thalamus [16–19]. For thalamic-cortical connectivity, discordant results were reported in different studies [18,19]. In this study, we investigated thalamic FC between thalamus and other brain regions by resting-state fMRI in patients with MS and healthy

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Table 1
Descriptive data of the study groups.

	RRMS	HC
Number of subjects	35	35
Mean age (range) [years]	38.1 (18–58)	35.6 (18–54)
Sex (M/F)	11/24	11/24
Median EDSS (range)	2.5 (1.0–6.0)	–
Median disease duration (range) [months]	43.7 (6–204)	–
Median T2 lesion load (range) [mm^3]	6225 (78–25481)	–

RRMS: relapsing–remitting multiple sclerosis; HC: healthy controls; EDSS: expanded disability status scale. See text for further details.

controls (HC), and correlated the FC changes with other MRI and clinical variables.

2. Materials and methods

2.1. Participants

We studied thirty-five patients with relapsing-remitting multiple sclerosis [20,21] (11 males, 24 females; mean age 38.1, SD 11.9). All subjects were assessed clinically by a single experienced neurologist (J.Y), who was unaware of the MRI results. The main demographic and clinical characteristics of the patients studied are reported in Table 1. None of the participating patients had been treated with MS-specific medications (e.g., interferon-beta or immunosuppressive therapies) within three months of the MR images being obtained. We choose 35 age- and sex-matched HC (mean age 35.6, SD 10.5) with no previous history of neurological disease and with normal findings on neurological examination. The subjects were all right-handed as measured by the Edinburgh Inventory [22]. The institutional review board of Xuanwu Hospital approved the study, and written informed consent was obtained from each participant.

2.2. MRI acquisition

Imaging was performed on a 1.5 T Siemens Sonata scanner in the Radiology Department, Xuanwu Hospital, Capital Medical University. A standard head coil with foam padding was used to restrict head motion. All the routine axial slices were positioned parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum, with an identical field of view (240 mm × 210 mm), matrix size (256 × 224), number of sections (30), section thickness (4 mm), and intersection gap (0.4 mm): (a) T2-weighted turbo spin echo (repetition time [TR] = 5500 ms, echo time [TE] = 94 ms, number of signals acquired = 3, echo train length = 11), (b) T1-weighted spin echo (TR/TE = 650/6, number of signals acquired = 3), (c) fluid-attenuated inversion recovery (FLAIR) (TR/TE = 8500/150, inversion time [TI] = 2200 ms, number of signals acquired = 3, echo train length = 8). Sagittal three-dimensional (3D) Volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) (TR/TE = 1970/3.9 ms, TI = 1100 ms, flip angle = 15°, FOV = 219 mm × 250 mm, matrix size = 256 × 256, slice thickness = 1.7 mm, voxel dimensions = 0.5 mm × 0.5 mm × 1.7 mm) images were also obtained. During resting-state fMRI, subjects were instructed to keep their eyes closed, to remain motionless, and to not to think of anything in particular. We used a gradient-echo echo-planar sequence sensitive to BOLD (Blood Oxygen Level Dependent) contrast to acquire functional images (TR = 2000 ms, TE = 60 ms, flip angle = 90°). Twenty axial slices were collected with 5 mm thickness, and a 2 mm gap. Resolution was 1.875 mm × 1.875 mm in-plane.

2.3. Thalamic and white matter lesion volume measurement

All visible lesions were identified from FLAIR and T2 images and manually extracted from T2-weighted scans using MRIcro software (http://www.cabiatl.com/mricro) including lesions in the thalamus. Next, the T2 lesion volume of each patient was calculated (shown in Table 1).

The whole thalamus was traced and saved as a mask from the coronal three-dimensional MPRAGE images by an experienced radiologist (Y.D, with 8 years experience), blinded to clinical information. The thalamic boundaries were determined manually using MRIcro, and left and right thalamus was saved as masks for further FC analyses. Raw thalamic volumes were normalized within each subject as a ratio to the intracranial volume. The resulting normalized thalamic volume was referred to as the thalamic fraction (TF). To test the reproducibility of our findings, twenty randomly chosen subjects (10 patients with MS and 10 HC) had thalamic segmentation repeated by the same observer (Y.D) one month later and by another experienced observer (Y.L, with 7 years experience in neuroradiology) to determine intra- and inter-rater reliability.

2.4. Resting-state functional MRI data analysis

2.4.1. Image preprocessing

All analyses were conducted using a statistical parametric mapping software package (SPM5, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes of the functional images were discarded to reach signal equilibrium and allow participants adaptation to the scanning noise. The remaining 229 fMRI images were first corrected for within-scan acquisition time differences between slices and then realigned to the first volume to correct for inter-scan head motions. No participant had head motion of more than 1.5 mm maximum displacement in any of the x, y, or z directions, or 1.5° of any angular motion throughout the course of scan. Next, we spatially normalized the realigned images to the standard echo-planar imaging template and resampled them to 3 mm × 3 mm × 3 mm. Subsequently, the functional images were spatially smoothed with a Gaussian kernel of 4 mm × 4 mm × 4 mm FWHW to decrease spatial noise. Following this, temporal filtering ($0.01\,Hz < f < 0.08\,Hz$) was applied to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise by using Resting-state fMRI Data Analysis Toolkit (http://resting-fmri.sourceforge.net). To further reduce the effects of confounding factors, we also used a linear regression process to further remove the effects of head motion and other possible sources of artifacts: (1) six motion parameters, (2) whole-brain signal averaged over the entire brain, (3) linear drift.

2.4.2. FC analysis

The left and right thalamic masks were co-registered to the functional MR images as the seed regions by using SPM5. For each subject and each seed region, we produced a correlation map by computing the correlation coefficients between the reference time series (computed from all the voxels within each ROI) and the time series from all other brain voxels. Correlation coefficients were normally transformed to z values using Fisher's r-to-z transform [23].

2.5. Statistical analysis

The individual z value was entered into a random effect one-sample t-test in a voxel-wise manner to determine brain regions showing significant connectivity to the left and right thalamus within each group. The z values were also entered into a random effect two-sample t-test to identify the regions showing significant differences in connectivity to the bilateral thalami between MS