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Cortical Thinning Correlates with Cognitive Change in Multiple Sclerosis but not in Neuromyelitis Optica

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Abstract
Objectives To compare spatial patterns of cortical thickness alterations in neuromyelitis optica (NMO) and multiple sclerosis (MS); and to investigate the correlations between cortical thinning and clinical variables in NMO and MS.
Methods We studied 23 patients with NMO, 27 patients with MS and 26 healthy controls (HCs). The global, brain region and vertex-based cortical thickness (CTh) were analysed and compared among the three groups. A general linear model was used to investigate the correlations between cortical thinning and clinical measures.
Results A limited number of cortical regions in visual cortex were found to be significantly thinner in NMO patients than in HCs. The MS patients exhibited more widespread cortical thinning compared with HCs, and significantly greater cortical thinning in the insula and the parahippocampus compared with NMO. The extent of cortical thinning in several brain regions correlated with cognitive measures in MS, but not in NMO.
Conclusions Neocortical thinning in NMO mainly affects visual cortex, while MS patients show much more extensive cortical thinning. Cognitive changes are correlated with cortical atrophy in MS not in NMO. The substrates of cognitive changes in MS and NMO could therefore be different.
Key Points
- *MS patients show much more extensive cortical thinning than NMO.*
- *Cortical thinning of insula and parahippocampus particularly distinguishes MS from NMO.*
- *Cognitive changes are correlated with cortical atrophy in MS but not in NMO.*

Keywords Multiple sclerosis · Neuromyelitis optica · Cortical thickness · Cognitive impairment

Abbreviations

CTh	Cortical thickness
HC	Healthy control
MS	Multiple sclerosis
NMO	Neuromyelitis optica
WM	White matter

Introduction

Neuromyelitis optica (Devic's disease) (NMO) is an inflammatory astrocytopathy and demyelinating disease of the central nervous system (CNS) that is characterised by severe attacks of the optic neuritis and myelitis, often without significant cerebral pathology seen on T2 or FLAIR sequences [1, 2]. However, brain abnormalities in NMO were shown in several studies using different magnetic resonance imaging

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(MRI) modalities [3–8]. Simple white matter diffusion measures of NMO patients, such as mean diffusivity histograms were reported as normal [5] or showed abnormalities in motor and visual systems only [9]. However, more advanced diffusion techniques reported significant changes in brain white matter (WM) in NMO, for example using tract-based spatial statistics [6] or small world network properties [10]. Whether brain atrophy occurs in NMO is controversial. Mild grey matter atrophy in frontal, temporal and insular regions was detected by voxel-based morphology (VBM) in one previous study [11], but not confirmed in others [12, 13].

Cortical thickness is a more reliable, direct and biologically significant measurement of atrophy than cortical volume due to the low variability in the cytoarchitectural structure of the grey matter [14, 15]. Measurements of cortical thickness can reflect the size, density and arrangement of cells. Measuring cortical thickness provides important information regarding regional integrity of the cerebral cortex, thus yielding new insights into disease pathology [16–19].Currently, there is only one study [20] that reported mild cortical thinning in the visual and sensorimotor cortex in NMO patients.

Cognitive impairment is a common co-morbidity of multiple sclerosis (MS) which detrimentally affects many aspects of daily life, with prevalence rates ranging from 43 % to 70 %, and cortical atrophy correlates with cognitive defects in MS [21]. In NMO, cognitive change has been reported [7], but the relationship between cortical atrophy and cognitive impairment in NMO has not previously been assessed. In the present study, we analysed global and regional cortical thickness (CTh) in NMO patients, and directly compared the findings with a cohort of MS patients and healthy controls (HCs), using high-resolution isotropic 3.0-T MRI data. Furthermore, we investigated the correlations between the identified cortical atrophy and clinical characteristics, including cognitive scores in both diseases.

Materials and methods

Participants

The institutional review board of Xuanwu Hospital approved the study and written informed consent was obtained from each participant. We consecutively recruited 23 NMO patients (3 men, 20 women; mean age 35.5 years, SD 10.8 years), and 27 relapsing-remitting MS (RRMS) patients (8 men, 19 women; mean age 33.2 years, SD 9.4 years) from the Department of Neurology in Xuanwu Hospital, Capital Medical University from January 2012 to September 2013. The RRMS diagnosis was made according to the modified McDonald criteria [22] and NMO diagnosis was determined according to the revised diagnostic criteria (absolute criteria: optic neuritis and myelitis, the presence of at least two of the following three additional criteria: (1) brain MRI results negative or non-diagnostic for MS at onset, (2) MRI evidence of a spinal cord T2 lesion of three or more vertebral segments, and (3) a serological test result positive for NMO antibodies [2]. All of the NMO patients were relapsing NMO and 18 NMO patients (78.3 %) were AQP4 antibody positive. Eighteen of the NMO patients had no white matter FLAIR or T2 hyperintensities identified by cerebral MRI and five had non-specific T2/FLAIR white matter lesions. None of the participating patients had been treated with disease-modifying medications in the 2 weeks before the MR images were obtained. The main demographic and clinical characteristics, including mini–mental state examination (MMSE), paced auditory serial addition test 3-seconds version (PASAT3), paced auditory serial addition test 2 (PASAT2), Expanded Disability Status Scale (EDSS) and disease duration of the patients studied, are reported in Table 1. We chose 26 sex- and age-appropriate HCs (9 men, 17 women; mean age 35.1 years, SD 11.3 years) with no previous history of neurological dysfunction and with normal findings on neurological examination and MRI (Table 1).

Image acquisition

Imaging was performed on a 3.0-T MR system (Trio Tim; Siemens, Erlangen, Germany) in the Department of Radiology, Xuanwu Hospital, Capital Medical University. A standard head coil was used with foam padding to restrict head motion. The routine axial slices were positioned to run parallel to a line that joins the AC-PC line of the corpus callosum, with an identical field of view (256 mm×256 mm), number of sections (35) and section thickness (4 mm). (1) Axial T2-weighted turbo spin echo (repetition time [TR]=5,000 ms, echo time [TE]=87 ms, number of signals acquired=1, echo train length=15, matrix size=256×256); (2) axial fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE=8,500/87 ms, inversion time [TI]=2,500 ms, number of signals acquired=1, matrix size=256×256); (3) sagittal three-dimensional (3D) volumetric T1-weighted magnetisation-prepared rapid acquisition gradient echo (MPRAGE) (TR/TE=1,600/2.13 ms, TI=1,000 ms, flip angle =9°, FOV=256 mm×224 mm, matrix size=256×224, slice thickness=1.0 mm, voxel dimensions=1.0 mm×1.0 mm×1.0 mm) images were obtained. The routine sequences (T2-weighted imaging and FLAIR) were used to identify brain lesions and 3D MPRAGE was acquired for cortical thickness measurement.

Cortical thickness measurement

We utilised a routine pipeline of the CIVET software (version 1.1.9; Montreal Neurological Institute at McGill University, Montreal, Quebec, Canada) to extract cortical thickness from the structural MR images. The flowchart of the software to

Table 1 Demographic and clinical characteristics[a]

N	MS 27	NMO 23	HC 26	*p* value /
Gender	8 M/19 F	3 M/20 F	9 M/17 F	0.21[b]
Age (years)	33.15±9.40 (11-49)	35.48±10.75 (17-56)	35.08±11.28 (21-57)	0.70[c]
Education (years)	13.96±2.70 (9-19)	13.43±2.89 (9-19)	13.85±3.29 (9-19)	0.81[c]
EDSS	3.33±1.45 (0-6.5)	4.52±1.76 (1-8)	/	0.01[d]
PASAT3	42.00±9.82 (29-57)[e]	43.62±7.40 (26-54)[e]	53.65±6.58 (29-59)	<0.01[c]
PASAT2	35.94±10.12 (21-58)[e]	33.46±8.22 (19-48)[e]	47.35±8.63 (22-57)	<0.01[c]
MMSE	26.60±1.51 (25-30)[e]	26.80±1.75 (23-29)[e]	29.87±0.34 (29-30)	<0.01[c]
Disease duration (years)	42.53±29.48 (0.4-10)	51.91±54.73 (0.2-17)	/	0.45[d]

MS multiple sclerosis, *NMO* neuromyelitis optica, *HC* healthy control, *EDSS* Expanded Disability Status Scale, PASAT3 Paced Auditory Serial Addition Test 3 seconds, *PASAT2* Paced Auditory Serial Addition Test 2 seconds, *MMSE* Mini Mental State Examination

[a] Data are presented as mean ± SD (range) except for *N* and *Gender*

[b] Chi-squared test

[c] Main effect of group in ANOVA

[d] Two-sample *t*-test

[e] $p<0.01$ compared with HCs in post-hoc *t*-test

evaluate the cortical thickness is shown in Fig. 1. Briefly, the original images were first registered to stereotaxic space with linear transformation, while the non-uniformity artefacts were corrected using the N3 algorithm [23]. Then the registered and corrected images were automatically segmented into grey matter, white matter, cerebro-spinal fluid and background using an advanced neural net classifier [24]. The inner and outer grey matter surfaces, with a total of 81,924 polygons (40,962 vertices each hemisphere) were then automatically extracted from each magnetic resonance (MR) volume using the constrained Laplacian-based automated segmentation with proximities (CLASP) algorithm [25]. Cortical thickness (CTh) was thus defined as the distance between linked vertices on the inner and outer surfaces [26]. Finally, a 20-mm smoothing was applied to improve sensitivity [27]. The cortical thickness measurement approaches have previously been validated with high sensitivity and reproducibility using both manual measurements [28] and simulation approaches [26]. Furthermore, this method has been applied to study neurological diseases such as multiple sclerosis [29], Alzheimer's disease [14, 30] and schizophrenia [31].

Statistical analysis

An analysis of covariate (ANCOVA) was employed to explore the CTh differences among the three groups. Age, gender and years of education were taken as covariates. We tested the mean CTh measurements of the whole brain, each of the hemispheres, all the 78 regions of interests from the surfaced-based Automated Anatomical Labeling (AAL) template, and the CTh on each vertex. The significance level for lobar CTh, AAL CTh and vertex-based comparisons was determined as $p<0.05$ after false discovery rate (FDR) correction. Furthermore, we employed the areas presenting significant main effect of group in CTh ANCOVA as a mask to test the correlation between cognitive scores and CTh at all the scales mentioned above. To do this, we constructed a general linear model, selecting CTh as the dependent variable, and clinical scores including cognitive scores as the independent variable and age, gender and years of education as covariates. All the vertex-based results were visualised using BrainNet Viewer software (version 1.4, http://www.nitrc.org/projects/bnv/).

Results

Demographic and neurological evaluations

As shown in Table 1, no significant differences were observed in age, gender and years of education among the three groups (RRMS, NMO and HC). The NMO patients showed higher EDSS than MS patients. The disease duration, PASAT3, PASAT2 and MMSE showed no significant difference between MS and NMO subjects ($p=0.45$, 0.63, 0.48 and 0.79 respectively). However, both patient groups revealed significantly lower scores of PASAT3, PASAT2 and MMSE compared with the HC group.

Global, hemispheric, lobe and brain regional cortical thickness differences

The mean CTh was significantly different among the three groups (MS, NMO, HC) ($p=0.0022$). The MS patients had

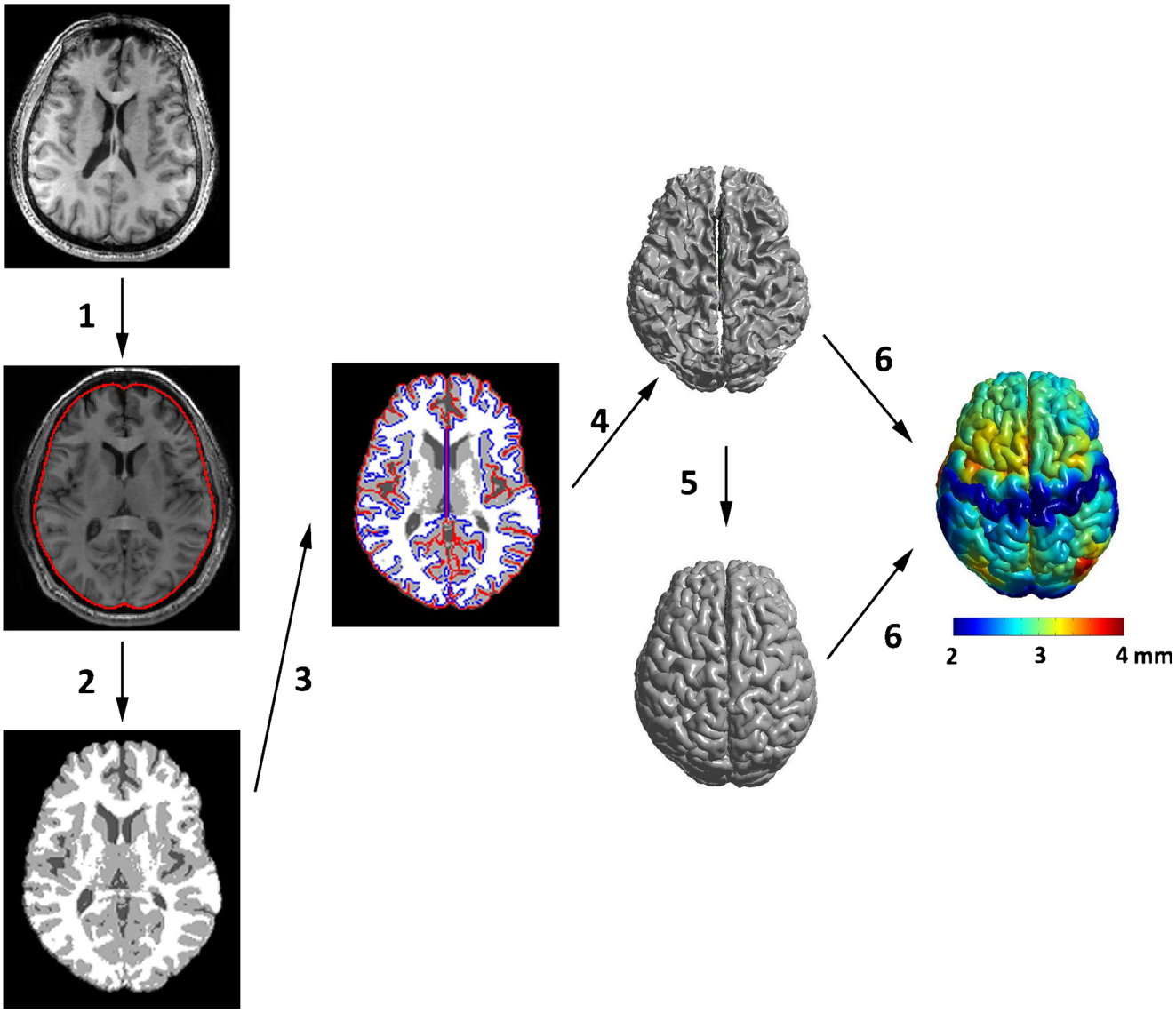

Fig. 1 Flowchart of CIVET software. The structural images were first corrected for non-uniformity and registered to stereotaxic space (*1*). Then the images were segmented (*2*) and the grey matter/white matter interface was extracted (*3-4*). The grey matter/CSF interface was sequentially determined by expanding the grey matter/white matter interface (*5*). Finally, the CTh was measured on each vertex and smoothed by a 20-mm surface-based kernel (*6*)

significantly thinner cortices (global measure) than NMO patients (p=0.046) and HCs (p=0.0005). Individual hemispheres showed similar results (left hemisphere: F-test p=0.0021, MS versus HC p=0.0005, MS versus NMO p=0.05; right hemisphere: F-test p=0.0013, MS versus HC p=0.0003, MS versus NMO p=0.033) (Fig. 2). Compared with HCs, the MS patients had widely distributed CTh thinning in bilateral temporal and occipital lobes, the left frontal lobe and the right parietal lobe, and in the right temporal lobe compared with the NMO group (p<0.05 FDR corrected, Table 2). The NMO group was no different to HCs at the global, hemispheric or lobar level, but a trend towards thinner cortex measures was observed in the left occipital lobe (p=0.023 uncorrected, p=0.18 FDR corrected). The analysis of AAL regional cortical thinning showed reduced CTh in brain regions located in temporal, occipital, frontal and parietal lobes in MS patients compared with HCs. Several regions also showed more severe thinning in MS compared with NMO, limited to the temporal and occipital lobes, while significant CTh thinning was only found in the left calcarine fissure and surrounding cortex (within the left visual cortex) in comparisons of NMO patients with HCs (p<0.05 FDR corrected, Table 3).

Vertex-wise cortical thickness differences

The vertex-wise ANCOVA revealed results in accordance with the above results at brain lobe and brain region levels. It is evident that the areas showing a significant difference in

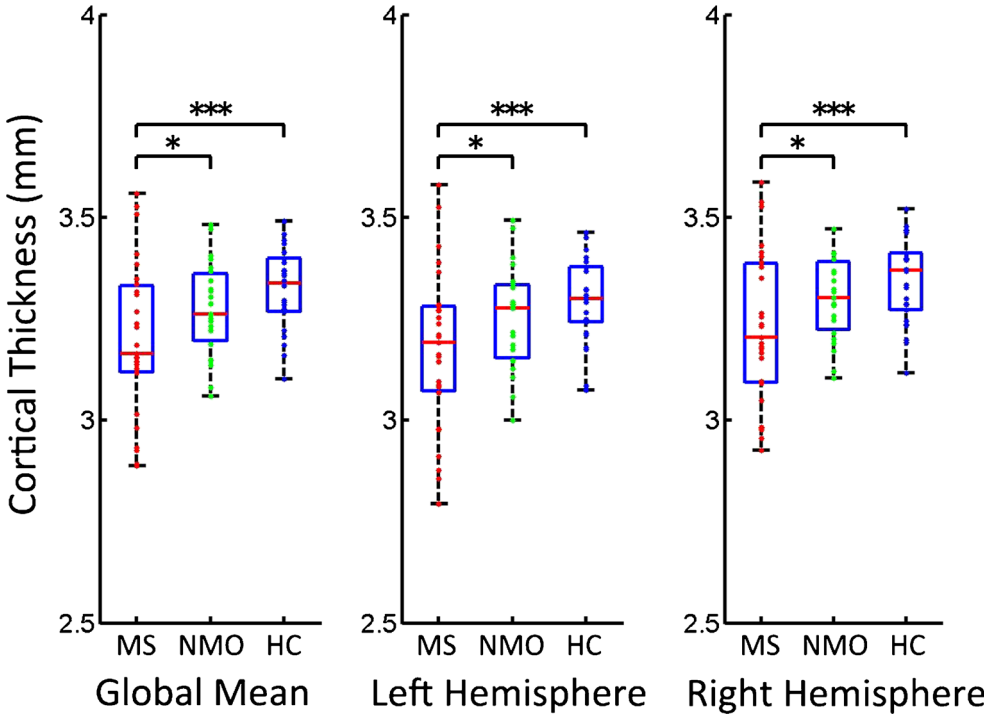

Fig. 2 Mean cortical thickness (CTh) of the subjects in MS, NMO and HC groups. The mean CTh of the whole cortical (*left*), the left hemisphere (*middle*) and the right hemisphere (*right*) are shown *** $p<0.001$, *$p<0.05$

CTh among the three groups ($p<0.05$, FDR corrected) were widely distributed in the cerebral cortex (Fig. 3a). MS patients had thinner cortices than the HC group in the bilateral occipital, medial temporal, left inferior frontal and the right parietal brain regions (Fig. 3b). The MS group also showed significant cortical thinning, compared with the NMO group, in the left parahippocampus, bilateral insula, and the left inferior occipital gyrus (Fig. 3c).The cortical thickness reduction found in the NMO group compared with the HC group was limited to the left middle occipital gyrus (Fig. 3d).

Association between CTh changes and clinical tests including cognitive scores in patients with NMO and MS

In MS patients, significant correlations between atrophy of the left parahippocampus, left fusiform and left superior frontal

Table 2 Comparisons of global, hemispheric and lobar CTh among MS, NMO and HC groups

	MS	NMO	HC	F-test	MS-HC	MS-NMO	NMO-HC
Global mean	3.20±0.19	3.27±0.12	3.32±0.10	6.66 (0.0022)*	-3.63 (0.00054)*	-2.03 (n.s.)	-1.41 (n.s.)
Left hemisphere	3.15±0.20	3.23±0.14	3.28±0.11	6.76 (0.0021)*	-3.66 (0.00048)*	-2.00 (n.s.)	-1.47 (n.s.)
Right hemisphere	3.16±0.19	3.24±0.10	3.29±0.11	7.32 (0.0013)*	-3.80 (0.00031)*	-2.17 (n.s.)	-1.43 (n.s.)
Left frontal lobe	3.24±0.20	3.30±0.13	3.35±0.11	4.32 (0.017)*	-2.94 (0.0045)*	-1.44 (n.s.)	-1.35 (n.s.)
Left parietal lobe	2.99±0.22	3.05±0.15	3.06±0.09	1.85 (n.s.)	-1.88 (n.s.)	-1.25 (n.s.)	-0.53 (n.s.)
Left temporal lobe	3.40±0.23	3.52±0.17	3.54±0.14	5.53 (0.0059)*	-3.14 (0.0025)*	-2.42 (n.s.)	-0.57 (n.s.)
Left occipital lobe	2.88±0.20	2.93±0.16	3.04±0.13	7.60 (0.0010)*	-3.86 (0.00025)*	-1.33 (n.s.)	-2.32 (n.s.)
Right frontal lobe	3.25±0.22	3.29±0.12	3.34±0.13	2.88 (n.s.)	-2.40 (n.s.)	-1.04 (n.s.)	-1.23 (n.s.)
Right parietal lobe	2.99±0.18	3.06±0.13	3.09±0.09	4.42 (0.016)*	-2.86 (0.0056)*	-2.05 (n.s.)	-0.67 (n.s.)
Right temporal lobe	3.41±0.23	3.55±0.13	3.57±0.13	7.77 (0.00090)*	-3.61 (0.00056)*	-3.07 (0.0031)*	-0.38 (n.s.)
Right occipital lobe	3.03±0.17	3.10±0.14	3.16±0.12	6.32 (0.0030)*	-3.55 (0.00069)*	-1.74 (n.s.)	-1.63 (n.s.)

The mean and standard deviation of global and lobar CTh in each group are shown

F values and *t* values were derived from ANCOVA of mean CTh of the whole cortex, both hemispheres and eight lobes (four in each hemisphere)

The *numbers in parentheses* are *p* values; *n.s.* non-significant

*$p<0.05$ after FDR correction

Table 3 AAL regions revealed significant CTh differences among MS, NMO and HC groups

Lobe	AAL region	MS	NMO	HC	F-test	MS-HC	MS-NMO	NMO-HC
Frontal lobe	Left inferior frontal gyrus, opercular part	3.32±0.30	3.41±0.19	3.52±0.10	7.04 (0.0016)	-3.74 (0.00038)**	-1.41 (n.s.)	-2.13 (n.s.)
	Left inferior frontal gyrus, triangular part	3.51±0.23	3.50±0.22	3.62±0.19	6.48 (0.0026)	-3.52 (0.00076)**	-0.96 (n.s.)	-2.36 (n.s.)
Occipital lobe	Right lingual gyrus	3.15±0.27	3.20±0.15	3.25±0.16	8.97 (0.00034)	-4.23 (0.000069)**	-2.01 (n.s.)	-2.01 (n.s.)
	Left calcarine	3.21±0.16	3.22±0.19	3.28±0.18	8.82 (0.00038)	-4.03 (0.00014)**	-0.80 (n.s.)	-3.00 (0.0037)**
	Left inferior occipital gyrus	3.21±0.19	3.28±0.16	3.32±0.12	8.55 (0.00048)	-3.89 (0.00023)**	-3.05 (0.0032)**	-0.65 (n.s.)
	Left fusiform gyrus	3.26±0.21	3.29±0.14	3.36±0.11	8.39 (0.00054)	-4.02 (0.00014)**	-2.54 (n.s.)	-1.28 (n.s.)
	Right fusiform gyrus	3.62±0.28	3.66±0.19	3.72±0.17	6.75 (0.0021)	-3.67 (0.00047)**	-1.77 (n.s.)	-1.71 (n.s.)
	Left lingual gyrus	3.09±0.24	3.14±0.17	3.26±0.10	6.56 (0.0024)	-3.62 (0.00055)**	-1.71 (n.s.)	-1.72 (n.s.)
	Right inferior occipital gyrus	3.45±0.32	3.54±0.22	3.60±0.18	5.42 (0.0065)	-3.27 (0.0017)**	-1.83 (n.s.)	-1.28 (n.s.)
	Right calcarine	3.47±0.33	3.53±0.22	3.54±0.19	5.08 (0.0087)	-3.09 (0.0028)**	-0.76 (n.s.)	-2.16 (n.s.)
	Left middle occipital gyrus	3.39±0.24	3.46±0.26	3.51±0.27	4.90 (0.010)	-3.03 (0.0035)**	-0.69 (n.s.)	-2.17 (n.s.)
Parietal lobe	Right supramarginalgyrus	3.09±0.25	3.10±0.22	3.13±0.24	8.60 (0.00046)	-4.11 (0.00011)**	-2.39 (n.s.)	-1.52 (n.s.)
	Right postcentralgyrus	3.43±0.30	3.51±0.17	3.53±0.18	5.36 (0.0068)	-3.06 (0.0031)**	-2.44 (n.s.)	-0.47 (n.s.)
Temporal lobe	Left parahippocampalgyrus	2.92±0.26	2.97±0.21	3.02±0.20	15.40 (0.0000029)	-5.26 (0.0000015)**	-4.00 (0.00016)**	-1.01 (n.s.)
	Right parahippocampalgyrus	2.86±0.27	2.97±0.20	2.94±0.19	12.25 (0.000028)	-4.94 (0.0000051)**	-2.01 (n.s.)	-2.66 (n.s.)
	Right heschlgyrus	3.26±0.20	3.33±0.17	3.35±0.14	9.10 (0.00031)	-3.98 (0.00017)**	-3.21 (0.0020)**	-0.58 (n.s.)
	Right insula	3.28±0.17	3.30±0.19	3.38±0.14	8.33 (0.00057)	-3.32 (0.0014)**	-3.64 (0.00052)**	0.46 (n.s.)
	Right superior temporal gyrus	3.03±0.35	3.07±0.28	3.15±0.23	7.11 (0.0015)	-3.60 (0.00059)**	-2.67 (n.s.)	-0.75 (n.s.)
	Left insula	3.68±0.21	3.67±0.23	3.76±0.21	5.82 (0.0046)	-3.30 (0.0015)**	-2.30 (n.s.)	-0.83 (n.s.)
Limbic system	Right anterior cingulate	3.30±0.25	3.37±0.23	3.46±0.22	6.20 (0.0033)	-3.50 (0.00080)**	-1.31 (n.s.)	-2.01 (n.s.)
	Left anterior cingulate	3.38±0.33	3.45±0.19	3.48±0.24	4.95 (0.0098)	-3.06 (0.0031)**	-2.06 (n.s.)	-0.85 (n.s.)

This table shows the mean and standard deviation of CTh of AAL regions in each group

F and *t* values were derived from ANCOVA. Only the regions revealing a significant difference among the three groups are presented

The *numbers in parentheses* are *p* values; *n.s.* non-significant

**$p<0.05$ after FDR correction

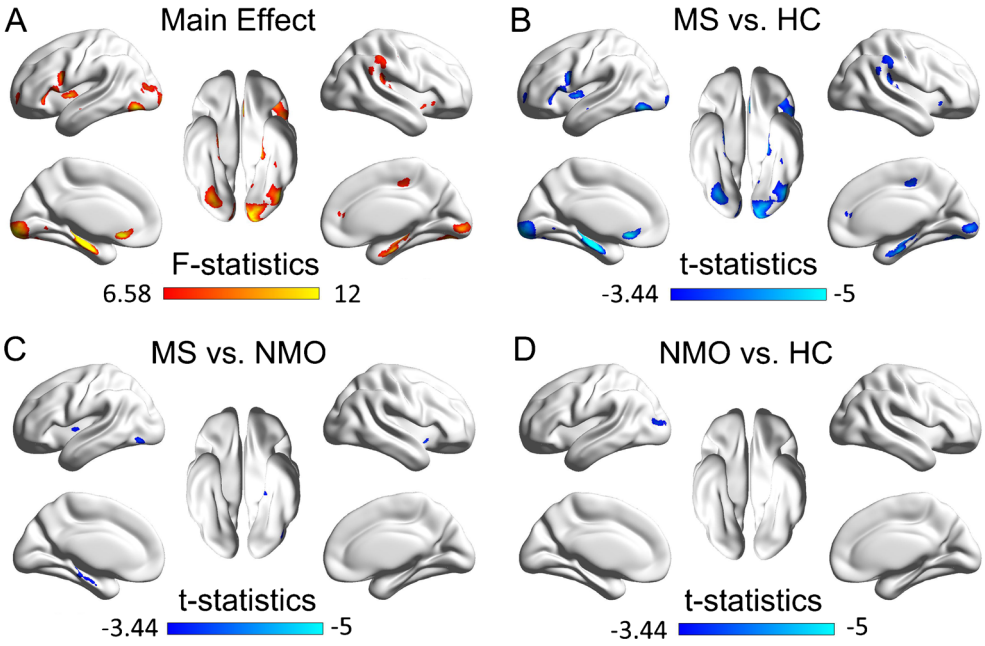

Fig. 3 Vertex-based CTh ANCOVA results after FDR correction ($p<0.05$). **a** F-value map depicting main effect of groups. **b** T-value map of post-hoc comparison between MS and HC. **c** *T*-value map of post-hoc comparison between MS and NMO. **d** *T*-value map of post-hoc comparison between NMO and HC. Age and gender were taken as covariates in ANCOVA

orbital gyri and both PASAT3 and PASAT2 ($p<0.01$, corrected for age, sex and educational status) were shown at the vertex level (Fig. 4a, b). No correlation with the cognitive changes was found at whole brain, lobe or AAL brain region level. A significant negative correlation between the disease duration and cortical atrophy was found in six brain regions (right calcarine, right Heschl's gyrus, right parahippocampal gyrus, right lingual gyrus, right insula and left anterior cingulate gyrus; all $p<0.01$) at the AAL brain region level and confirmed at the vertex level (Fig. 4c). No significant correlation was identified between EDSS and cortical thinning in MS.

In NMO patients, no significant correlations were observed between cortical atrophy and disease duration, EDSS or cognitive test at either AAL brain region or vertex level.

Discussion

In this study, we investigated global and regional grey matter changes in relatively well-matched NMO and MS patients and HCs by measuring CTh. We measured the CTh at five size levels: global mean CTh, average hemisphere CTh, average

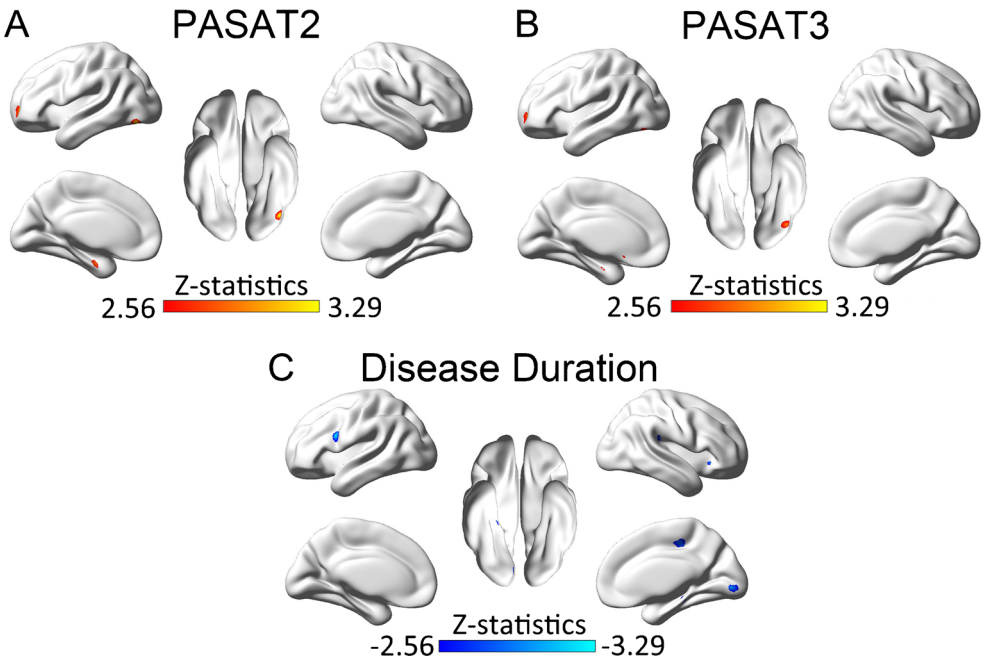

Fig. 4 Correlations between vertex-based CTh and clinical variables including PASAT2, PASAT3 and disease duration in patients with MS

lobe CTh, brain regional CTh, and vertex-wise CTh. Compared with the controls, no significant cortical thinning was observed in the NMO patients at global, hemispherical and lobar level. However, at the brain region and vertex-wise level, a limited number of cortical regions in visual cortex were found to be significantly thinner in NMO patients than HCs. These findings are consistent with previous studies of cortical volume loss in NMO using either the VBM method [11] or the cortical measurement method using Freesurfer software [20, 32]. Visual cortex thinning in NMO is most likely secondary to the severe optic nerve involvement in this disease. A recent study from von Glehn et al. [32] found a correlation between retinal nerve fibre layer (RNFL) thinning and pericalcarine cortical thickness, which supports the hypothesis of retrograde and anterograde neurodegeneration as the cause of GM atrophy in NMO.

In contrast, the MS patients exhibited widespread cortical thinning compared with HCs. This is consistent with previous studies using either cortical thickness [17, 18] as a measurement or the VBM method [11, 33] of assessing cortical volume loss. The current study extends previous studies by demonstrating the spatial patterns of cortical thinning in all three groups using the same software and imaging equipment.

Two recent neuropathological studies revealed different pathological changes in NMO cerebral cortex. One study revealed an absence of cortical demyelinating lesions, but widespread astrogliosis and neuronal pathology in cerebral cortex [8], while the other showed both inflammatory demyelinating events characterised by pattern-specific loss of AQP4 immune activity and cortical neurodegeneration in NMO [34]. While these might seem discordant with our results and some other previous MRI findings assessing brain atrophy in NMO [11, 20], MRI examinations are typically performed in patients with mild to modest disease burden and pathological studies are usually conducted in end-stage disease, assessing long-term pathological outcomes. Alternatively, current MRI techniques may be not sensitive enough to detect all the pathological findings.

Interestingly, subtle widespread white matter damage or atrophy was observed in several previous studies in NMO [6, 13, 35], contrasting with the very limited cortical thinning shown in our study, which could argue for predominant white matter involvement in NMO. Among many possible explanations for differential involvement of grey and white matter in NMO, expression of different isoforms of AQP, or differential blood brain barrier (BBB) permeability between grey and white matter are very plausible [36, 37].

The MS patients showed reduced global cortical thickness and widespread cortical thinning in many brain regions involving all the lobes, bilaterally. The pathological substrates of cortical thinning include cortical demyelination, neuronal loss, and secondary degeneration from white matter lesions [38]. Compared to NMO patients, cortical atrophy in MS patients was much more widespread and severe, showing a distinct pattern of cortical thickness changes. Interestingly, the largest differences between CTh in MS and NMO were in the insula and the parahippocampus, confirming results on one previous comparative study using VBM [11]. Furthermore, a previous study also showed that highly significant focal atrophy in temporal cortex occurred early in the MS disease course [18], and early insular and parahippocampus atrophy could therefore be a key feature distinguishing MS and NMO.

Interestingly, significantly reduced cognitive performance, including MMSE, PASAT2, PASAT3, was found in NMO patients, of a similar magnitude to MS patients, matched for age, disease duration and educational level. This cognitive change was correlated with areas of reduced cortical thickness in MS patients, in the left parahippocampus, left fusiform and left superior frontal orbital gyri. No such associations were found in NMO. Our study therefore suggests that the pathological substrate of impaired cognition in MS and NMO could be different; specifically that cognitive change is linked to cortical atrophy in MS but not in NMO. We believe that altered cognition in NMO may be correlated to widespread subtle abnormalities in white matter as reported by us and others [6, 13, 35], and/or similar subtle abnormalities in grey matter, for instance abnormalities on magnetic transfer ratio and diffusion histogram derived metrics [5]. Larger, longitudinal studies correlating cognitive change with advanced MRI measures will be required to better understand the evolution of relevant clinico-pathological correlations and identify the MRI biomarkers for monitoring cognitive impairment in MS and NMO. On the other hand, our study provides further evidence that cognitive change in MS is linked to cortical atrophy [39, 40], especially frontal and temporary atrophy, and that medical intervention reducing atrophy progression could reduce cognitive change, a concept that will need to be proven in large prospective studies.

Limitations

The present study had several methodological limitations. First of all, the sample size was relatively small. The significance and reliability of the results would be improved by enrolling more subjects, and also by comparing the NMO patients in different subgroups: those with brain lesions vs without brain lesions; NMO-IgG positive vs negative; cognitive impairment vs cognitive preserved. Secondly, subcortical grey matter regions are structurally different from cortical regions—they do not have an inner surface of grey matter—so the estimation of thickness by the method we used is not applicable to subcortical grey matter regions such as the hippocampus, thalamus and caudate, which are known to be affected early in MS. Finally, the cognitive assessment of the participants in the current study only includes MMSE and

PASAT, and a more systematical cognitive evaluation—for example, using Minimal Assessment of Cognitive Function in MS (MACFIMS) will be performed in a planned future study.

In conclusion, limited cortical thinning in NMO was found mainly in the visual cortex, while MS patients showed much more extensive cortical thinning. The main difference of cortical atrophy between MS and NMO was located in the insula and parahippocampus, which could potentially help distinguish these two diseases. Cognitive changes are correlated with cortical atrophy in MS and not in NMO, implying the substrates of cognitive changes in MS and NMO may be different.

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