Correlates of executive functions in Multiple Sclerosis based on structural and functional MRI – insights from a multicentre study

Original article

Advances in Knowledge:

- Thalamic volume and thalamic activation best predict information processing speed in Multiple Sclerosis (R^2=0.527).
- Increase in thalamic activation tends to correlate with worse cognitive performance (r=-0.410, p=.065, age corrected).
- Such increases in activation may thus be maladaptive.

Implications for Patient Care: This study highlights the benefits of a concomitant use of structural and functional imaging to shed light on the brain-behaviour relationship in the evolution of executive deficits in Multiple Sclerosis. These results might inform future targeted interventions to prevent or at least delay cognitive decline.

Summary Statement: Thalamic volume together with thalamic activation best serve as correlates of information processing speed in Multiple Sclerosis when compared to other predictive variables.

Abstract

Purpose: To study the concomitant use of structural and functional Magnetic Resonance Imaging (MRI) correlates to explain information processing speed (IPS) and executive functions (EF) in Multiple Sclerosis (MS) in a prospective multi-centre study.

Materials and Methods: Local ethics approval was obtained at all sites and all subjects gave written informed consent. Twenty-six relapsing-remitting MS (RR-MS) patients and 32 healthy controls from four centres underwent structural and functional MRI including a go/no-go task and neuropsychological assessment. Subtests of the Brief Repeatable Battery of Neuropsychological Tests, the Wisconsin Card Sorting Test and the performance with the functional MRI paradigm were used as estimates of IPS/EF. Activation of the thalamus and the inferior frontal gyrus (pars triangularis), thalamic volume, T2 lesion load, and age were used to explain IPS/EF function in regression models.

Results: Compared to controls, patients showed increased activation in a frontoparietal network including both thalami during the execution of the go/no-go task. Patients had decreased thalamic volume ($p<0.001$). Thalamic volume ($\beta=0.606$, $p=0.001$) together with thalamic activation ($\beta=-0.410$, $p=0.022$) best predicted IPS/EF and explained 52.7% of the variance in IPS/EF.

Conclusion: This current study highlights the potential of a combined use of functional and morphological parameters to explain IPS/EF in RR-MS patients, and confirms the central role of the thalamus as a relay station in executive functioning.

Introduction

Multiple sclerosis (MS) may lead to cognitive deficits already in the earliest stages of the disease (1), affecting up to 60% of the patients (2). Frequently impaired domains include memory, executive functions (EF), attention, and speed of information processing (IPS) (2,3). Cumulative evidence (2,4,5) corroborates the notion that deficits in memory and EF are strongly related to deficits in IPS, which constitutes a basic cognitive process subserving higher-order cognitive functions. IPS incorporates the abilities to maintain and manipulate information in the brain on-line and the speed with which information can be processed. A general slowing in IPS has been reported in MS, even when speed was not an explicit component of the neuropsychological test (5). Therefore, IPS constitutes a major hallmark for the cognitive status of MS patients deserving to be better characterized.

Despite their fundamental impact on the daily life of MS patients, the structural and functional abnormalities underlying these cognitive deficits have not yet been fully elucidated and MRI correlates of the cognitive status are a matter of current research. Structural brain imaging studies consistently found associations between cognitive deficits and whole brain volume (1,6–8), brain T2-lesion load (T2-LL) or location of T2 lesions in strategic white matter (WM) regions (9,10). Studies examining regional cerebral atrophy reported stronger associations with cognition, particularly highlighting thalamic atrophy as predictor of cognitive decline in MS (10,11). The thalami constitute relay stations involved in higher cortical, motor, sensory, and integrative functions, and thus play a significant role in EF, attention, and memory. Specifically, an association between IPS and thalamic atrophy in MS has been reported (12).

Besides structural imaging, functional MRI (fMRI) gained considerable interest in the characterisation of cognitive function in MS (13,14). Recently, increased functional connectivity

between the thalamus and the inferior frontal gyrus (pars triangularis, IFGpt) has been shown to correlate with cognition in MS (14). The complementary value, if present, of thalamic and IFGpt activation, thalamic volume and T2-LL for IPS/EF in MS patients has not been determined so far, although this would provide useful pieces of information to ultimately identify correlates in the evolution of cognitive deficits. We thus tested the hypothesis that functional in combination with morphological changes represent key determinants of IPS/EF in MS patients in a multicentre study using multimodal MRI data.

Materials and Methods

Sites and subjects. Twenty-six MS patients and 32 healthy controls (HC) were prospectively scanned at four European academic sites of the MAGNIMS (Magnetic Resonance Imaging in Multiple Sclerosis) network (www.magnims.eu) between 03/2010 and 06/2011. The inclusion criteria required all subjects to be right-handed (15) and aged between 20 and 55 years. In addition, patients had to fulfil the following criteria: a diagnosis of relapsing-remitting MS (16), no relapse or corticosteroids within the previous three months prior to scanning, an Expanded Disability Status Scale (EDSS) (17) score assessed at the time of the scanning by experienced neurologists of ≤4 (CE and ??? with ??? and ??? years of experience, respectively), and no clinically evident upper right limb impairment. Local ethics approval was obtained at all sites and all subjects gave written informed consent.

Data from four patients and five HC had to be excluded from the final analyses due to motion artefacts (n=3 patients/1 control), insufficient quality (n=1patient/2 controls) or scanner artefacts (n=0 patient/2 controls). The final dataset used for analyses thus comprised 22 MS patients (9 female, 13 male, median age 39.5 years) with a median disease duration of 6.3 years and a

median EDSS of 2.0 and 27 HC (13 female, 14 male, median age 33.6 years). Demographic and clinical data of all subjects are summarized in **Table 1**.

MRI data acquisition. Brain MRI scans were obtained using magnets operating at 3.0 Tesla at all sites (center 1: Philips Intera; centers 2 and 4: Siemens Trio; center 3: GE Signa). In all the subjects, the following sequences were acquired during a single session: a) 160 volumes of a single-shot gradient-echo EPI-sequence (TR=3000 ms, TE=30 ms, FA=90°, matrix size=128×128, FOV = 240 mm, slice thickness = 4 mm, number of slices =30) for fMRI; b) a dual-echo turbo-spin-echo (TSE) scan: TR = ranging from 4000 to 5380 ms, TE_1 = ranging from 10 to 23 ms, TE_2 = ranging from 90 to 102 ms, echo train length (ETL) = ranging from 5 to 11, 44 contiguous, 3-mm thick axial slices, parallel to the AC-PC plane, with a matrix size = 256x192 and a FOV = 240x180 mm^2 (recFOV = 75%); and c) a magnetization prepared 3D T1-weighted scan: TR = ranging from 5.5 to 8.3 ms (for GE/Philips scanners) and from 1900 to 2300 ms (for Siemens scanners); TE = ranging from 1.7 to 3.0 ms; flip angle ranging from 8° to 12°, 176 to 192 sagittal slices with thickness = 1 mm and in-plane resolution = 1x1 mm^2.

Structural image analyses. The analysis of structural MRI data was done centrally at center 1 by experienced observers (MR with ??? years of experience, respectively). T2-LL was measured on dual-echo TSE scans, using a local thresholding segmentation technique (Jim 5.0, Xinapse System, Leicester, UK). Normalized brain (NBV), WM (NWMV) and GM (NGMV) volumes were measured on 3D T1-weighted scans using the SIENAx software (18), after T1-hypointense lesion refilling (19). The thalami were segmented from the 3D T1-weighted images using the FIRST tool from the FMRIB Software Library (20). Normalized thalamic volumes were calculated from the FIRST output using the SIENAx scaling factor (18).

Neuropsychological Tests. Trained psychologists (MK and ??? with 9 and ??? years of experience, respectively) tested the patients on the day of scanning using the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), which assesses information processing speed, (sustained) attention and concentration, memory, visuospatial learning, verbal learning, and verbal fluency, and the Wisconsin Card Sorting Test (WCST) assessing higher executive abilities.

To obtain a value for IPS/EF, the mean of the z-transformed scores of the Symbol Digit Modalities Test (SDMT, total number correct), Paced Auditory Serial Addition Test (PASAT, total number correct), WCST (total number of perseverative errors, switched polarity) and the total number of correct button presses during the fMRI task was calculated. All four tests are commonly used in MS research and together reflect a wider spectrum of EF/IPS than could be obtained using a single parameter only.

Additionally, handedness was obtained using a questionnaire (15). All but one patient was right handed and the data of one subject for handedness was missing.

FMRI paradigm: In the go/no-go stimulus-response discrimination task, subjects had to react as fast as possible to a predefined target, either a cross or a square, pressing a button with their right index-finger. The paradigm, implemented as block design (160 volumes, duration: 480s), consisted of eight 30s active conditions and eight interspersed 24s rest phases where an exclamation mark was presented. A 3s non-verbal instruction presented prior to each active run indicated the target. In every active block, one stimulus constituted the target while the other stimulus required response suppressing, ended by a 3s “stop”-signal. Targets, shown for 300ms, had varying inter-stimulus intervals (ISI) to modulate severity (1000, 2000, 2500, 1000, 2500, 1500, 2000, and 1500ms). Reaction times (RT), omission errors (no response although required), commission errors (false response without adequate cue), and the proportion of correct responses

were recorded. Prior to scanning, participants were familiarized with the paradigm outside the scanner.

FMRI data analyses. The analyses were carried out using tools from the fMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl) (MK and CE with 9 and 12 years of experience, respectively). The following pre-statistic processing was applied during first-level analyses: motion correction (21) and spatial smoothing using a Gaussian kernel of full width half maximum of 5 mm, and high pass temporal filtering Gaussian-weighted least squares straight line fitting, sigma=30.0s. FMRIB's Improved Linear Model served for time-series statistical analysis with local correction for autocorrelation. Higher-level analysis was done using mixed effects (FMRIB's Local Analysis of Mixed Effects, stage 1). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z>2.3$ and a corrected cluster significance threshold of $p=0.05$. In first level analyses, effects of all go/no-go blocks vs. rest were determined for each subject. Registration was checked visually. In second level mixed-effects analyses, mean activation maps for go/no-go blocks vs. rest at group level were calculated for patients and HC separately. In third level mixed-effects analyses, contrasts between patients and HC were obtained. To identify areas specifically associated with IPS/EF, the z-transformed IPS/EF scores of MS patients were correlated with the functional time-course.

Functional regions of interests (ROI). To determine the predictive value of functional variables, the posterior part of the thalamus (PPT), and the right IFGpt were selected (14). The thalamic ROI was created based on the binarized Oxford Thalamic Connectivity Probability Atlas (22) (threshold: 25), separately for the left and right hemisphere. The right IFGpt ROI was based on a data driven approach. A 5mm spherical ROI at the MNI coordinates 26, 22, 28 was chosen. These coordinates formed the peak voxel in the biggest cluster of the two-sample t-test between

MS patients and HC (MS>HC), consistent with the area of specific importance reported by Schoonheim et al. (14). Beta scores of the ROIs of the filtered 4D dataset were extracted and used for regression analysis.

Statistical analyses: SPSS (version 21) was used for statistical analyses (MK with 14 years of experience). We fitted a taxonomy of linear regression models to the data. Predictors used were beta scores of the time-series of the PPT and the IFGpt during the execution of the fMRI-task, mean bilateral thalamus volume, and T2-LL. All analyses were corrected for age. Regressions were exclusively done with patients' data.

Effects of centre: To examine a possible bias induced by centre, data from centres were compared considering age, EDSS, disease duration, sex and education. Also, two-sample t-tests comparing centres considering the functional imaging data of healthy controls were performed.

Results

Structural MRI findings. Compared to HC, patients had decreased thalamic, GM and total brain volumes. No significant differences existed for WMV (**Table 2**).

Cognitive performance. **Table 3** summarizes the neuropsychological test performance of MS patients, and the behavioural performance during the fMRI go/no-go task of study participants in the scanner. There were no significant differences between patients and HC concerning the

performance in the go/no-go task executed in the scanner regarding the three outcome measures (reaction time, omission and commission mistakes).

Functional MRI findings. MS patients and HC showed a widespread pattern of activations comprising bilateral mesial (pre-SMA) and dorsolateral prefrontal, parietal, insular, basal ganglia, and cerebellar regions (**Figure 1, Table 4**). When compared to HC, patients showed increased activations in frontal (including the inferior frontal gyrus (pars triangularis), IFGpt), parietal and temporal cortices, as well as in the thalami, and the right caudate nucleus (**Figure 2**). No areas were significantly more strongly activated in HC compared to patients. To explore a potential functional coupling between the posterior part of the thalamus (PPT) and the IFGpt, a partial correlation was calculated, but this showed no significant correlation (r=0.306, p=n.s.; corrected for age).

In MS patients, correlation analysis between the BOLD response and speed of information processing / executive functions (IPS/EF) performance revealed a significant negative association with signal change with the paradigm in the thalami and frontal, parietal, and occipital areas, but not with the IFGpt **(Figure 3).**

Taxonomy of linear regression models: Linear regression, using each variable individually as predictor for IPS/EF, revealed a high predictive value for T2-LL (41.5% explained variance, p=.002), and normalized thalamic volume (39.5% explained variance, p=.002). Beta scores of the PPT showed a trend towards significance (16.5% explained variance, p=.065). The largest amount of variance was explained using T2-LL, thalamic volume and PPT activation as predictors in one model (55.0% explained variance). However, due to multi-collinearity (correlation between T2-LL and thalamic volume: r=-0.553, p=.008) these models need to be interpreted cautiously. Therefore, the best model predicting IPS/EF comprised thalamic volume

and PPT activation (52.7% explained variance). Moreover, worse IPS/EF performance was associated with increased thalamic activation. The beta scores of the IFGpt revealed no association with IPS/EF (7.7% explained variance, p=.113). See **table 5** for the full taxonomy.

Effects of centre: Considering the effects of centres, no significant bias was found for age ($F(3,45)=0.432$, p=.731), EDSS ($F(3,18)=0.601$, p=.622), disease duration ($F(3,18)=1.072$, p=.386), or sex ($X^2(3, N=22)=4.133$, p=.256), but for education ($F(3,44)=5.765$, p=.002). To assess whether there was any consistent variation in fMRI activation between study centres, this parameter was used as grouping variable. Potential effects of sites on functional activation were assessed using data from HC. Analyses did not show any significant differences between centres.

Discussion

Several brain areas have been implicated as important for cognitive function in MS (23), with a particular role suggested for the thalamus. However, investigations combining insights from structural and functional MRI are rare. In this study, we found that thalamic atrophy together with increased thalamic activation of MS patients best predicted worse speed of information processing and executive functions when compared to other predictive variables.

. This underpins the sensitivity of these complementary measures in explaining such complex cognitive behaviour. These results might inform future targeted interventions to prevent or at least delay cognitive decline, and might allow monitoring targeted pharmaceutical drug-trials aiming to maintain or improve cognitive functions in a longitudinal design.

The strategic significance of the thalamus for higher cortical functions, attention, motor and sensory functions has led to the common designation as a gateway to the cerebral cortex (11). As

pathology within the thalamus is frequently observed in MS, its morphological, metabolic and histopathological changes have been extensively examined in the past (24–27), and the negative impact of such changes on cognitive functions has repeatedly been reported (12,24,26). However, its functional architecture has rarely been scrutinized (13,14,28). A recent seed-based resting state study examined thalamic functional network changes and their association with PASAT performance (13) and found, similar to our study, that thalamic functional connectivity increases in MS patients are associated with worse behavioural performance. Another study examined morphological parameters and changes in functional connectivity within a group of MS patients heterogeneous with respect to cognitive function (preserved, mild and severe cognitive impairment) (14). They reported that increases in functional connectivity between the thalamus and other areas of the brain manifested only in severely impaired patients. Interestingly, the strongest correlation was found between the functional increase of the thalamus with the IFG and decreased cognitive functions. The authors concluded that thalamic functional connectivity changes (especially of the thalamus with the IFG) together with thalamic atrophy and a diffusion-weighted measure best predicted cognitive status of cognitively impaired MS patients (46% explained variance). We extend the above findings by showing that thalamic volume and PPT activation can already serve as an objective correlate in less severely cognitively impaired MS patients. Also, equivalent to Schoonheim et al. (14), we found increased activation in the IFGpt in patients when compared to controls during the execution of the go/no-go task. In contrast, we could not reveal any association between IFGpt and IPS/EF performance or identify a functional coupling between the IFGpt and the PPT. We therefore speculate that this coupling occurs at a later stage of the disease causing more pronounced cognitive problems. However, longitudinal studies monitoring the functional coupling and their impact on cognitive function are needed.

Previous functional imaging studies reporting on hyperactivation of task-specific brain areas in MS patients were interpreted to constitute an adaptive behaviour of the brain to compensate for disease related damage (29). However, this interpretation has now been challenged by several studies (14,28) including this one, reporting on an inverse relationship between increased activation and cognitive performance. In particular, the negative impact of increased thalamic activation on cognition has now repeatedly been shown and indicates that thalamic hyperactivation more likely reflects mal-adaption (13) rather than adaptive reorganization. A recent study examining microstructural brain alterations observed that normal appearing cortico-thalamic white matter tracts as well as thalamic sub-regions showed structural deterioration associated with cognitive disabilities (24). This underscores the notion that the pathology in MS targets GM rich structures such as the thalamus (11) and that adaptive processes, if at all, are only restrictedly possible within the affected structure.

This study also has limitations. Due to strict quality control of the imaging data, data from four patients and five controls had to be excluded. This may have reduced statistical power, but was necessary for data reliability. Subsequently, the sample size examined might be considered as comparatively small. However, the network activated by the go/no-go task in this group of MS patients and healthy controls acquired across multiple centres is consistent with the activations defined in a prior single-centre study in a different group of patients and controls (30). The results of the current study therefore can be considered as robust. As a pecularity, an almost equal number of male and female patients participated in our study, in contrast to the known preponderance of females affected by RR-MS. While we do not know the reasons for this and gender effects generally appear possible, we failed to find evidence in the literature to support this. Also, no neuropsychological assessment was performed in the control subjects. We therefore could not directly compare patient and control performance, but instead used the standardized

norms. Due to time efficiency and our main interest on the correlations between patients' cognitive performance and imaging parameters, cognitive assessment of the controls was not part of the protocol Moreover, subjects in the control group were younger and had more years of education. However, the main result of our study is based on patient data, and therefore not affected by these imbalances. On the other hand, this makes the assumption quite safe that the control group was indeed cognitively normal. Furthermore, a role of cortical lesions and T1 hypointense white matter lesions (indicating severe focal tissue destruction) for cognitive deterioration has been demonstrated in patients with RR-MS (23). Such parameters should therefore be integrated in subsequent investigations. Regarding the segmentation of deep GM structures and MS lesions, alternative analytical approaches have been suggested recently (32, 33), which might also be considered in further work. Lastly, a longitudinal design including repeated fMRI to more closely examine the correlates of EF/IPS over longer periods of follow-up appears desirable for future studies, although this poses additional challenges.

In summary, this study shows that a multi-modal approach, combining morphological and functional parameters is feasible, also in a multi-centric setting and may well be suited for exploring IPS/EF in MS patients. However, the predictive value of this information needs to be confirmed in longitudinal studies.

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Table 1. Characteristics of the entire cohort of MS patients and HC and per study site.

	Centre 1		Centre 2		Centre 3		Centre 4		Total (MS) N=22	Total (HC) N=27	p
	MS N=4	HC N=4	MS N=7	HC N=8	MS N=5	HC N=5	MS N=6	HC N=10			
Mean age [y (SD)]	43.0 (6.6)	34.7 (11.2)	39.4 (9.7)	32.4 (5.4)	39.6 (6.1)	34.6 (10.5)	37.1 (10.2)	33.7 (6.5)	39.5 (8.3)	33.6 (7.4)	0.012
male/female	2/2	2/2	3/4	3/5	3/2	2/3	5/1	7/3	13/9	14/13	0.616
EDSS median (range)	1.5 (1.0-2.5)	n.A.	2.0 (1.0-4.0)	n.A.	2.0 (1.0-2.0)	n.A.	2.5 (0-3.5)	n.A.	2.0 (0-4)	n.A.	n.A.
Median DD y (range)	5.0 (3-20)	n.A.	5.0 (2-8)	n.A.	10.6 (8-12)	n.A.	5.4 (3-20)	n.A.	6.3 (2-20)	n.A.	n.A.
Education [y (SD)]	11.0 (2.8)	16.7 (0.5)	17.0 (0.8)	18.3 (1.6)	12.2 (3.4)	13.8 (2.8)	12.1 (0.8)	17.3 (2.7)	13.5 (3.2)	16.8 (3.7)	<0.001

MS: Multiple Sclerosis, HC: healthy controls, y: years, SD: standard deviation, EDSS: Expanded Disability Status Scale, DD =disease duration, n.A.: not applicable

Table 2. Main structural MRI findings from healthy controls and patients with multiple sclerosis.

		Mean	SD	p
Normalized grey matter volume (cm^3)	HC	0.841	0.058	.016
	MS	0.786	0.093	
Normalized white matter volume (cm^3)	HC	0.714	0.039	.159
	MS	0.688	0.077	
Normalized total brain volume (cm^3)	HC	1.555	0.082	.016
	MS	1.474	0.129	
Thalamus mean volume (cm^3)	HC	8.687	0.941	.000
	MS	7.226	0.121	
T2-LL (cm^3)	MS	14.24	18.72	n.A.

HC = healthy controls, MS = multiple sclerosis patients

Table 3. Neuropsychological test performance (raw scores) of MS patients, and behavioural performance during the fMRI go/no-go task of study participants.

	Mean	**SD**	**min-max**
BRB-N			
Long Term Storage	46.3	12.3	24-65
Consistent Long Term Retrieval	34.4	19.7	5-65
Spatial Recall Test	18.3	5.3	7-28
SDMT	40.8	13.6	11-81
PASAT (3-sec)	35.5	13.5	13-57
Selective Reminding Test (dr)	8.3	2.8	2-12
Spatial Recall Test (dr)	6.7	2.3	2-10
Word List Generation	20.9	6.3	10-34
WCST			
Number of correct items	72.2	9.5	50-87
Number of errors	26.2	20.0	5-78
Number of perseverative errors	15.3	12.4	4-57
Number of perseverative responses	14.8	17.1	0-71
Go/nogo (mean ± SD)	**HC**	**MS**	**p**
Reaction time, s	0.389 ± 0.07	0.385 ± 0.05	0.820
Number of omission mistakes	1.15 ± 4.11	2.27 ± 4.71	0.680
Number of comission mistakes	0.85 ± 2.98	3.09 ± 4.75	0.198

BRB-N = Brief Repeatable Battery of Neuropsychological Tests, WCST = Wisconsin Card Sorting Test; SDMT = single digit modality test; PASAT = paced auditory serial addition test; dr = delayed recall.

Table 4. Cluster table displaying local maxima in the go/no-go task of healthy controls (HC), MS patients and the group difference (MS>HC).

Mean HC	Z	x	y	z	hemisphere, area
	4.64	52	4	36	R precentral gyrus
	4.22	-14	-16	8	L thalamus
	4.18	26	36	0	R insular cortex
	3.94	-18	6	16	L caudate
	3.93	-20	2	16	L caudate
	3.91	48	12	0	R frontal operculum cortex
	5.8	6	-64	-12	R lingual gyrus
	5.14	-6	-78	-14	L lingual gyrus
	4.79	4	-58	-10	R cerebellum
	4.71	4	-58	-16	R cereblllum
	4.71	0	-52	2	R cerebellum
	4.58	4	-74	-12	R cerebellum
	4.33	-6	0	54	L supplementary motor area
	4.29	-4	2	50	L supplementary motor area
	3.72	12	6	50	R supplementary motor area
	3.71	4	10	50	R supplementary motor area
	3.67	8	8	48	R paracinculate gyrus
	3.64	6	6	44	R anterior cingulate cortex
	3.59	-22	-58	38	L superior parietal lobule
	3.46	-36	-20	50	L precentral gyrus
	3.45	-30	-30	38	L white matter
	3.38	-40	-8	56	L precentral gyrus
	3.36	-30	-12	24	L white matter
	3.34	-32	-6	56	L precentral gyrus
Mean MS					
	5.7	8	-66	-16	R cerebellum
	5.43	4	-60	-10	R cerebellum
	5.2	-2	8	42	L anterior cingulate cortex
	5.04	14	-50	-20	R cerebellum
	5.01	-38	-8	46	L precentral gyrus
	5	0	-52	-18	R cerebellum
MS>HC					
	3.78	56	22	28	R inferior frontal gyrus
	3.67	44	36	6	R frontal pole
	3.61	42	42	2	R frontal pole
	3.49	32	38	12	R frontal pole
	3.48	48	52	0	R frontal pole
	3.44	12	14	-6	R nucleus accumbens
	4.05	-48	-14	8	L Heschl's gyrus
	3.56	-38	-14	42	L precentral gyrus

3.48	-46	-38	10	L	planum temporale
3.47	-44	-6	54	L	precentral gyrus
3.46	-46	-12	52	L	precentral gyrus
3.39	-50	-6	18	L	postcentral gyrus
4.17	46	-82	-2	R	lateral occipital cortex
3.49	18	-90	2	R	occipital pole
3.4	16	-98	-4	R	occipital pole
3.34	22	-94	10	R	occipital pole
3.32	20	-94	-4	R	occipital pole
3.25	28	-76	-6	R	occipital fusiform gyrus
3.84	40	-36	12	R	planum temporale
3.42	52	-40	36	R	supramarginal gyrus
3.28	48	-42	22	R	supramarginal gyrus
3	62	-42	4	R	middle temporal gyrus
2.92	50	-42	8	R	middle temporal gyrus
2.87	64	-36	6	R	superior temporal gyrus
3.94	10	-22	-12	R	brain stem
3.92	-20	-32	0	L	thalamus
3.79	-16	-32	12	L	thalamus
3.28	-8	-24	-4	L	thalamus
3.26	10	-24	-4	R	thalamus
3.24	-14	-18	-4	L	thalamus
3.22	20	10	54	R	superior frontal gyrus
3.15	18	12	48	R	superior frontal gyrus
3.07	16	8	44	R	supplementary motor area
3.04	2	32	34	R	paracinculate gyrus
2.93	6	14	38	R	anterior cingulate cortex
2.89	8	20	30	R	anterior cingulate cortex
3.31	-34	18	14	L	frontal operculum cortex
3.04	-22	16	8	L	white matter
3	-40	24	20	L	inferior frontal gyrus
2.89	-38	38	18	L	frontal pole
2.88	-34	14	16	L	frontal operculum cortex
2.88	-50	26	24	L	inferior frontal gyrus

Table 5. Fitted taxonomy of linear regression models to the data.

			Stand. beta	p	R^2corr
model 1	predictor 1	PPT-activation	-0.425	.065	0.165
	predictor 2	age	-0.137	.534	
model 2	predictor 1	IFGpt	-0.270	.213	0.077
	predictor 2	age	-0.308	.158	
model 3	predictor 1	thalamus volume	0.615	.002	0.395
	predictor 2	age	-0.169	.343	
model 4	predictor 1	T2-LL	-0.623	.002	0.415
	predictor 2	age	-0.202	.248	
model 5	predictor 1	PPT-activation	-0.410	.022	0.527
	predictor 2	thalamus volume	0.606	.001	
	predictor 3	age	-0.011	.950	
model 6	predictor 1	IFGpt	-0.174	.325	0.396
	predictor 2	thalamus volume	0.585	.004	
	predictor 3	age	-0.179	.319	
model 7	predictor 1	PPT-activation	-0.200	.322	0.416
	predictor 2	T2-LL	-0.553	.007	
	predictor 3	age	-0.135	.466	
model 8	predictor 1	IFGpt	-0.191	.268	0.424
	predictor 2	T2-LL	-0.598	.002	
	predictor 3	age	-0.209	.229	
model 9	predictor 1	PPT-activation	-0.370	.125	0.148
	predictor 2	IFGpt	-0.166	.442	
	predictor 3	age	-0.161	.474	
model 10	predictor 1	T2-LL	-0.417*	.037.*	0.501
	predictor 2	thalamus volume	0.389*	.053*	
	predictor 3	age	-0.151*	.354*	
model 11	predictor 1	PPT-activation	-0.304*	.104*	0.550
	predictor 2	thalamus volume	0.462*	.022*	
	predictor 3	T2-LL	-0.270*	.185*	
	predictor 4	age	-0.040*	.811*	
model 12	predictor 1	IFGpt	-0.156*	.333*	0.501
	predictor 2	thalamus volume	0.367*	.068*	
	predictor 3	T2-LL	-0.407*	.042*	
	predictor 4	age	-0.159*	.328*	
model 13	predictor 1	PPT-activation	-0,389	.040	0.504
	predictor 2	IFGpt	-0.063	.705	
	predictor 3	thalamus volume	0.596	.002	
	predictor 4	age	-0.022	.900	
model 14	predictor 1	PPT-activation	-0.149	.476	0.408
	predictor 2	T2LL	-0.549	.008	
	predictor 3	IFGpt	-0.155	.391	
	predictor 4	age	-0.158	.403	

PPT: posterior parietal part of the thalamus, IFGpt: inferior frontal gyrus, pars triangularis, *the coefficient estimates of this linear regression might be changed erratically due to

multi-collinearity; the results for individual predictors might therefore be not valid.

Figure 1. Mean activation of healthy controls (HC) and multiple sclerosis (MS) patients during the execution of the go/no-go task (z=2.3, p=.05; R = right side of the brain).

Figure 2. During execution of the fMRI task, MS patients showed increased activation in a fronto-parieto-temporal network including the inferior frontal gyrus pars triangularis (IFGpt) and the thalami when compared to controls (group contrast MS patients vs. controls, labelled MS>HC), whereas controls did not show increased activation in any area when compared to the patients (z=2.3, p=.05).

Figure 3. Bold response in the thalami, frontal, parietal and occipital areas negatively correlated with information processing speed and executive function in MS patients (z=2.3, p=.05).