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Deep grey matter MRI abnormalities and cognitive function in relapsing-remitting multiple sclerosis

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ABSTRACT

Although deep grey matter (GM) involvement in multiple sclerosis (MS) is well documented, in-vivo multi-parameter magnetic resonance imaging (MRI) studies and association with detailed cognitive measures are limited. We investigated volumetric, diffusion and perfusion metrics in thalamus, hippocampus, putamen, caudate nucleus and globus pallidum, and neuropsychological measures, spanning 4 cognitive domains, in 60 relapsing-remitting MS patients (RRMS) (mean disease duration of 5.1 years, median EDSS of 1.5) and 30 healthy controls. There was significantly reduced volume of thalamus, hippocampus and putamen in the RRMS patients, but no diffusion or perfusion changes in these structures. Decreased volume in these deep GM volumes in RRMS patients was associated with a modest reduction in cognitive performance, particularly information processing speed, consistent with a subtle disruption of distributed networks, that subserve cognition, in these patients. Future longitudinal studies are needed to elucidate the influence of deep GM changes on the evolution of cognitive deficits in MS.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS), affecting both white matter (WM) and grey matter (GM). Demyelination is variably associated with axonal transection, degeneration, volume loss and eventual CNS atrophy (Trapp and Stys, 2009). The involvement of deep GM structures in MS is of particular interest, because the thalamus, limbic and striatal structures are involved in all the major functional circuits in the brain and provide points of convergence across multiple cortical, limbic, brain stem and cerebellar systems. A focus on deep GM structures therefore offers the potential to unmask associations between functional status and early pathophysiology.

Deep GM hypointensity measures on T2-weighted scans and lesions on double inversion recovery have been correlated with disability (Zhang et al., 2007; Calabrese et al., 2013) and cognitive impairment (Brass et al., 2006; Calabrese et al., 2013). Automated methods for segmentation of deep GM structures, including FSL (Patenaude et al., 2011) or FreeSurfer (Fischl et al., 2002), reveal volume loss in MS deep GM structures, particularly the thalamus (Houtchens et al., 2007; Calabrese et al., 2010; Schoonheim et al., 2012; Minagar et al., 2013). This volume loss probably reflects neuronal loss, and provides a plausible marker of neurodegeneration in deep GM, which could be due to either local pathology or to Wallerian degeneration along white matter pathways that traverse the deep GM (Haider et al., 2014). In relapsing-remitting MS (RRMS), reduced deep GM volume has been associated with fatigue (Calabrese et al., 2010), and decreased thalamic volume with cognitive impairment (Houtchens et al., 2007; Schoonheim et al., 2012).

Diffusion tensor imaging (DTI) detects the Brownian motion of water molecules to assess microstructural integrity in the brain. It enables comparison of metrics such as mean diffusivity (MD), a measure of overall water diffusion, and fractional anisotropy (FA), a scalar measure of the variation in direction of diffusion. DTI studies consistently show increased MD, but the findings in FA have been inconsistent with either increased (Tovar-Moll et al., 2009) decreased (Ceccarelli et al., 2007) or no change (Griffin et al.,

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2001; Cecarelli et al., 2007; Tovar-Moll et al., 2009), in the cortical and subcortical normal-appearing GM of MS patients. Inconsistent FA metrics were particularly true for the thalamus (Ciccarelli et al., 2001; Filippi et al., 2001), where increased MD has been associated with cognitive impairment (Benedict et al., 2013). Such discrepancies could be attributed to variations in the underlying pathology, which in turn may vary at different stages of the disease, or to a more severe cognitive impairment of the patients under study (Schoonheim et al., 2015) or even to methodological considerations (Sbardella et al., 2013). DTI-derived diffusion metrics in principal GM structures was used in the current study to assess deep GM changes in a homogeneous group of established RRMS patients.

In addition, reduced cerebral blood flow has also been described in deep GM structures of RRMS patients (Inglse et al., 2007, 2008; Varga et al., 2009; Debernard et al., 2014; Francis et al., 2013). This measure may reflect neuronal metabolic dysfunction and compromised cerebral vasculature, beyond neuronal loss.

A combination of different MRI techniques in a single, well-characterised cohort of MS patients may provide insight into the nature of deep GM abnormalities in-vivo. Previous multi-modality MRI study (Cappellani et al., 2014) to investigate the deep GM DTI abnormalities in 285 MS patients reported that deep GM DTI alterations were related to WM lesion and atrophy but not to cortical atrophy. We previously identified regions of reduced GM perfusion in the absence of volume loss in RRMS patients with a short disease duration (<5 years) (Debernard et al., 2014). However, that study did not focus on deep GM nuclei and did not include RRMS patients with longer disease durations. Bearing in mind that previous neuroimaging studies on the association between cognitive impairment and deep GM structures have often recruited a mixed-type MS population or only a restricted range of MRI metrics (Houtchens et al., 2007; Batista et al., 2012; Mesaros et al., 2012; Cappellani et al., 2014; Schoonheim et al., 2015), our recruited cohort was composed of only well-characterized RRMS patients with a disease duration of up to 15 years. Moreover, all of our patients underwent volumetric, diffusion and perfusion MRI to compare deep GM in RRMS to a matched group of controls. We then examined whether MRI metrics in this group of RRMS patients were associated with neuropsychological performance assessed using a battery of 14 cognitive tests, spanning four cognitive domains.

2. Methods

2.1. Subjects

Inclusion criteria for the study included a diagnosis of relapsing-remitting multiple sclerosis (revised McDonald criteria 2010) with a disease duration between 0 and 15 years and age between 20 and 51 years ($N=60$). Exclusion criteria were a diagnosis of primary or secondary progressive multiple sclerosis, a MS relapse within the preceding 30 days and steroid treatment within the preceding month. Any patients with a history or signs of other central nervous system disorder such as head injury, cerebrovascular disease, brain surgery or tumour, or severe depression, as measured by the Beck Depression Inventory (BDI-II), were excluded. In addition, patients with English as a second language or a diagnosis of dyslexia were also excluded. Thirty healthy individuals, with no previous history of neurological disorders or major psychiatric illness, served as a control group. Appointments for neurological, neuropsychological and MRI assessments were scheduled over 1 month in three visits. The study was approved by the Lower South Regional Ethics Committee of New Zealand, and informed consent was obtained from all participants, prior to assessments.

2.2. Neurological tests

Neurological assessment was performed by an experienced neurologist (DFM) and included relapse history and disability assessment using the Expanded Disability Status Score (EDSS). Multiple sclerosis severity score (MSSS) was derived, based on EDSS score and disease duration for each MS patient. Pre-morbid IQ was estimated with the Wechsler Test of Adult Reading (WTAR).

2.3. Neuropsychological assessments

Participants received neuropsychological assessments by trained examiners (SVS, CG, JRO). Tests that covered 4 cognitive domains were used (Strauss et al., 2006). Executive function was assessed with the Delis–Kaplan Executive Function System [D–KEFS] letter fluency, category fluency, category switching and Stroop colour-word interference tests (Delis et al., 2001). Working memory, attention and processing speed was assessed with the D–KEFS Stroop colour naming, D–KEFS Stroop colour word reading, Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT). Episodic learning (acquisition) and memory (recall) was assessed with the Brief Visual Memory Test-Revised (BVMT; Benedict, 1997), and the California Verbal Learning Test-II Short Form (CVLT-II SF; Delis et al., 2000). Visuoperceptual and visuospatial function was assessed with the Judgment of Line Orientation (JLO; Benton, et al., 1983) and Rey Complex Figure Test copy (RCFT; Meyers and Meyers, 1995). The overall profile of the RRMS group was also assessed by identifying instances of mild cognitive impairment (MCI). As in the wider literature, MCI status was defined as two or more deficits at the level of 1.5 SD below standardised normative age- and sex-adjusted data (Schinka et al., 2010; Litvan et al., 2012). These impairments were required within a single cognitive domain, as this is superior in terms of stability and association with neuropathology than criteria based on a single deficit scores across domains (Jak et al., 2009; Loewenstein et al., 2009).

2.4. Image acquisition

All scans were acquired in a single session on a 3T General Electric HDxt scanner (GE Healthcare, Waukesha, WI) with an eight-channel head coil. MRI acquisitions, including lesion characterization, volumetric, diffusion and perfusion imaging, are displayed in Fig. 1 and sequence details are provided in an e-supplement file. Subjects were requested to remain still during scans, and to close their eyes but remain awake during the perfusion imaging sequence.

2.5. Image pre-processing and analysis

2.5.1. MS lesion load and filling

MS lesions were manually outlined using Jim software (Jim 4.0 Xinapse System Leicester, UK) on T2 FLAIR and automatically filled with a lesion filling program on IR-SPGR images (Chard et al., 2010) to avoid misclassification during subsequent tissue segmentation. After lesion filling, images were visually inspected to confirm accuracy.

2.5.2. Structural images

2.5.2.1. Global GM and WM segments. Data pre-processing and analysis were performed using VBM8, a toolbox of SPM8 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience Group, London, UK) in Matlab 7.10.0 (R2010a, Mathworks, Natick, MA, USA) to obtain WM and GM segments. Structural images were intensity bias corrected, tissue classified and registered using linear and non-linear transformations

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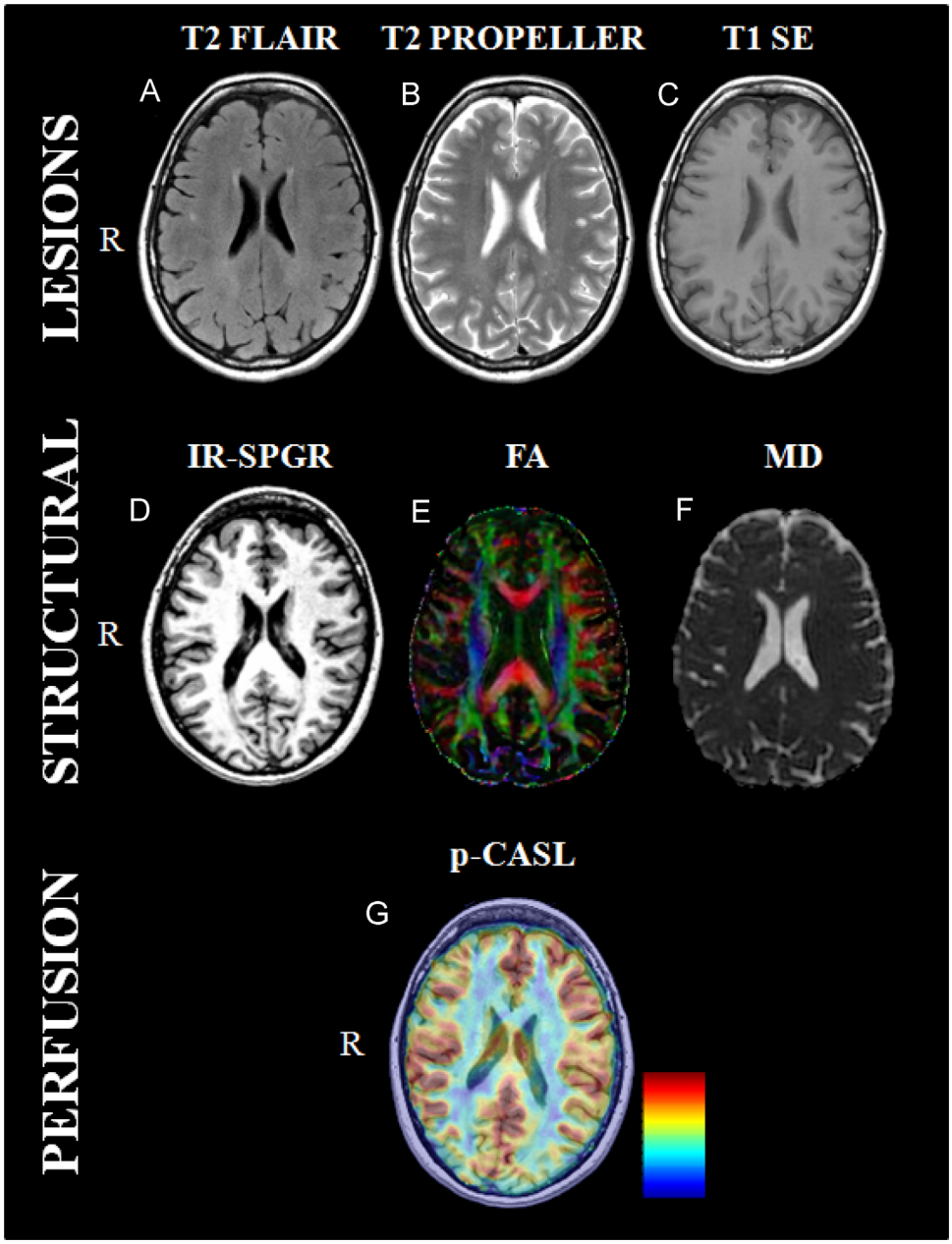

Fig. 1. MR images obtained for an early RRMS patient, including (A) T2 FLAIR, (B) T2 PROPELLER, (C) T1 SPIN ECHO for lesion characterisation, (D) T1-weighted inversion-prepared spoiled gradient recalled echo (IR-SPGR) for volumetric imaging, (E) fractional anisotropy (FA), (F) mean diffusivity (MD) for diffusion imaging and (G) pseudo-continuous arterial spin labelling (p-CASL) for perfusion imaging.

(Diffeomorphic Anatomical Registration Through Exponential Lie algebra), within a unified model (Ashburner and Friston, 2005). Visual inspection was performed to correct any tissue misclassification. Grey matter and white matter volumes were then calculated in subject space, obtained from the text files produced from the VBM8 process.

2.5.2.2. Normalised brain volume (NBV). After lesion filling, brain tissue volume, normalised for subject head size, was estimated using SIENAX (Smith et al., 2004) implemented in FSL 5.0.4 (FMRIB group, University of Oxford, UK). Steps included the following: 1) brain extraction from the individual IR-SPGR data, 2) co-registering brain images to MNI152 template, using affine transformation, and 3) tissue segmentation with partial volume estimation to derive total brain volume. A volumetric scaling factor was computed from normalised and un-normalised brain volumes, and used as a normalisation for head size in deep GM volumes (Schoonheim et al., 2012).

2.5.2.3. Deep GM volumes. Segmentation of deep GM structures was performed using FIRST, a toolbox of FSL. FIRST performs registration, segmentation based on Bayesian appearance (Patenaude et al., 2011) and boundary corrections (De Jong et al., 2008) to produce segmented thalamus, hippocampus, putamen, caudate nucleus, globus pallidum, nucleus accumbens and amygdala. These nuclei were verified visually (Fig. 2), and their raw and normalised volumes were calculated. Deep GM volume was normalised by correcting for head size (Schoonheim et al., 2012).

2.5.3. Diffusion and perfusion images

2.5.3.1. Diffusion metrics. Diffusion-weighted images were corrected for motion and eddy current distortion using FSL and brain-

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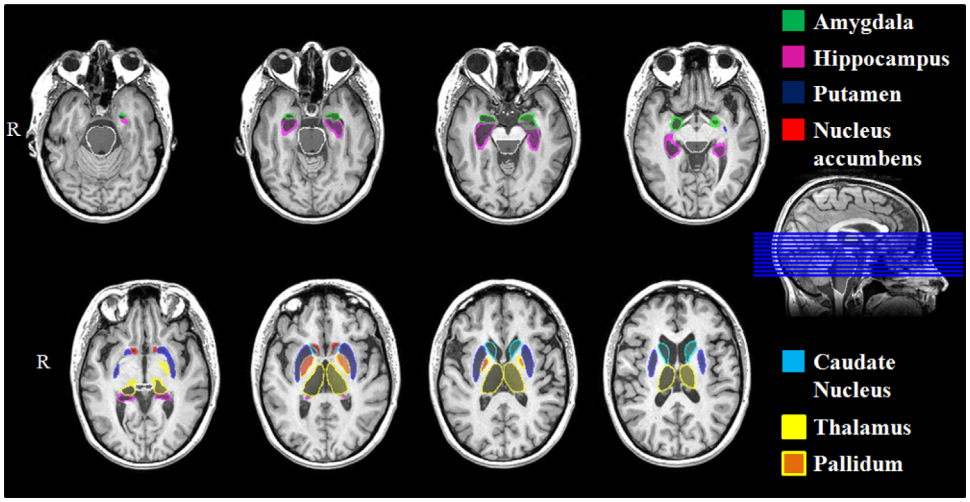

Fig. 2. Example of deep grey matter segments obtained on a healthy control using FIRST segmentation. The 7 deep GM structures (thalamus, hippocampus, putamen, caudate nucleus, globus pallidum, nucleus accumbens and amygdala) were overlaid onto the corresponding structural image.

extracted using BET. The diffusion tensor was calculated at each voxel using DTIFIT, producing fractional anisotropy (FA) and mean diffusivity (MD) images.

2.5.3.2. Diffusion and perfusion analysis. Diffusion (FA, MD) and perfusion images were coregistered to IR-SPGR images using SPM8 with visual inspection to detect coregistration errors (Fig. 3). Mean FA, MD and perfusion measurements were extracted from each segmented deep GM structure. Given the resolution of p-CASL ($3.75 \times 3.75 \times 5\ mm^3$), perfusion measurements in the small amygdala and nucleus accumbens were not considered accurate, and we only report MRI metrics (volume, diffusion and perfusion) in global WM, global GM, thalamus, hippocampus, putamen, caudate nucleus and globus pallidum (Fig. 4).

2.6. Statistical analysis

Statistical tests were performed using R software (version 2.15.2, R core team, 2012), and the level of significance was set at $p \leq 0.05$, for all tests.

2.6.1. Demographic comparisons between RRMS and control groups

These measures were compared in controls vs. RRMS using *t*-tests or Mann-Whitney test (for non-parametric measures).

2.6.2. Cognitive differences between RRMS and control groups

The difference between the RRMS and control groups for each neuropsychological test was assessed using ANCOVA, covarying for premorbid-IQ (WTAR). Cognitive scores were based on age- and gender-scaled normative data. In additional analysis, the BDI-II score was added as a covariate to determine whether depression symptoms influenced the findings.

2.6.3. MRI differences between RRMS and control groups

Differences between the RRMS and control groups for volume, diffusion (MD and FA) and perfusion metrics for global WM and GM and each deep GM structure was assessed using ANCOVA with age, gender and premorbid-IQ (WTAR) as covariates.

2.6.4. Relation of deep GM nuclei metrics with cognition in RRMS

When significant group differences (RRMS versus controls) were present in deep GM nuclei, we assessed the associations

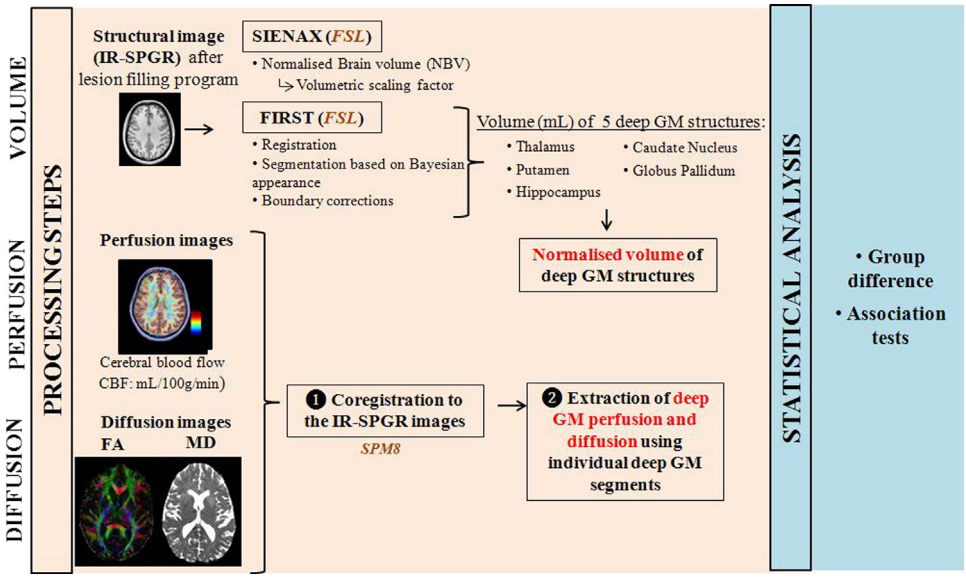

Fig. 3. Processing steps for the measurement of volume (ml), perfusion (CBF: cerebral blood flow in ml/100 g/min) and diffusion (FA: fractional anisotropy; MD: mean diffusivity in $mm^{-2}\ s^{-1}$) in 5 deep grey matter (GM) structures.

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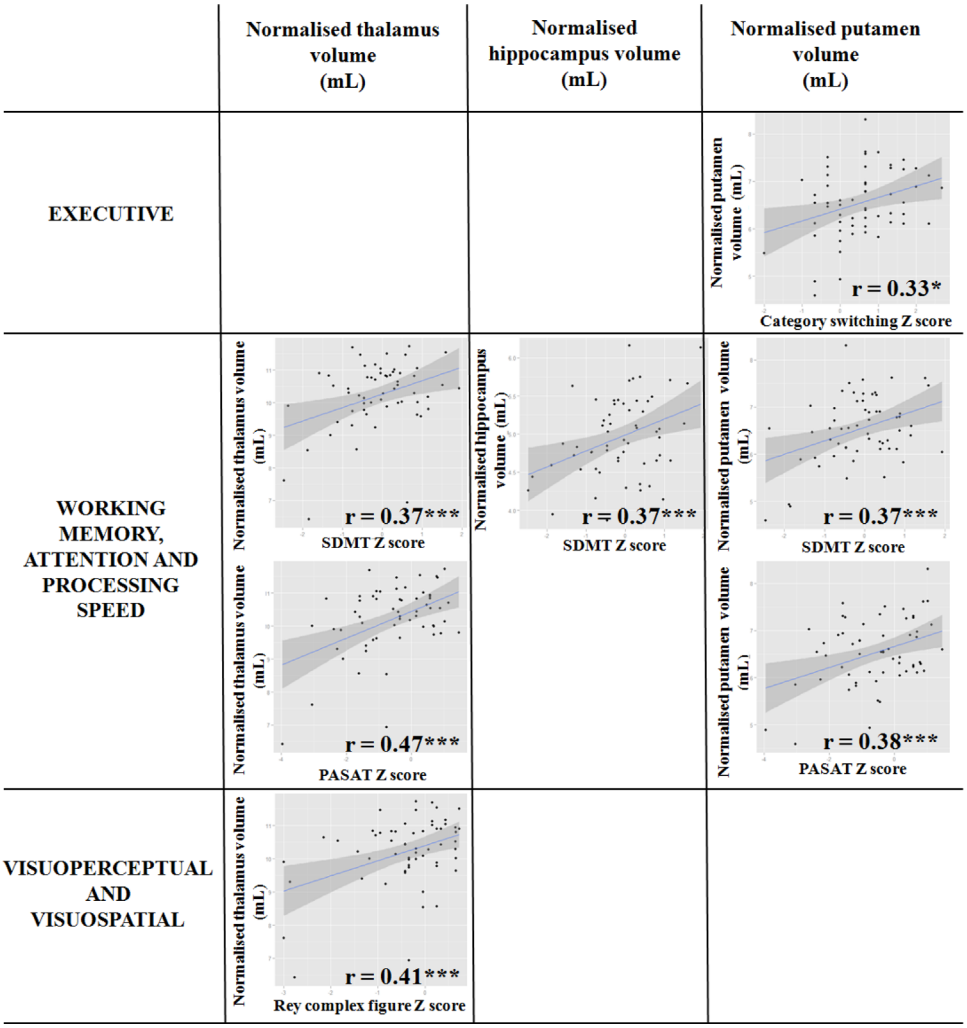

Fig. 4. Graphs showing visually the association between normalized thalamus, hippocampus and putamen volumes (ml) and cognitive *Z* scores in the RRM cohort. Correlation analyses were performed using Pearson product–moment correlation coefficient (*r*) and results are depicted when *p* Values are significant after Bonferroni correction ($^{*}p \leq 0.05$; $^{***}p \leq 0.01$).

between deep GM metrics and neuropsychological scores using 1) Pearson correlation coefficient in RRMS (with Bonferroni correction), followed by 2) multiple linear regression using premorbid IQ, disease duration and Beck depression inventory (BDI-II) as covariates in the model. A step-down regression approach was used to summarise the associations between deep GM metrics and neuropsychological assessments.

2.6.5. *Relation of deep GM nuclei metrics and WM lesion loading RRMS*

We investigated for associations between deep GM metrics and WM lesion load using the Pearson correlation coefficient (with Bonferroni correction).

3. Results

3.1. *Demographic variables*

There were no significant differences between RRMS and controls, although a larger number of depressive symptoms were endorsed by the RRMS group (Table 1). The EDSS and MSSS data showed that the RRMS patients generally experienced mild neurological impairment (Table 1). Ten RRMS patients were receiving disease-modifying medications (beta interferon or glatiramer acetate)

Table 1
Clinical and demographic features of 30 healthy controls and 60 relapsing-remitting (RRMS) patients included in the study.

	Healthy controls	RRMS patients	Group effect *p*-Value (df)
N (female: male)	30(22:8)	60(45:15)	
Mean age, years (range, SD)	34.7(19–51;10.3)	37.9(20–51;7.6)	0.10(88)
Mean premorbid-IQ, WTAR (SD)	107.6(7.0)	104.1(9.2)	0.08(88)
Mean disease duration, years (median, SD)	–	5.1(3.0,4,0)	–
Mean BDI-II (SD)	4.5(5.2)	8.4(6.1)	$< 0.01^{*}$
Median EDSS (mean, SD, range)	–	1.5(1.7,1.2,0–4.5)	–
Mean MSSS (SD)	–	2.8(1.9)	–

SD: Standard deviation; WTAR: Wechsler Test of Adult Reading; BDI: Beck Depression Inventory; EDSS: Expanded Disability Status score; MSSS: MS severity score.

* Indicates significant *p* Values ($p \leq 0.05$) and df the degrees of freedom for *t*-tests.

3.2. *Cognitive assessment*

The RRMS group was generally similar to the healthy controls or demonstrated only mild impairments, with significantly poorer

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Table 2
Mean *z* score (standard deviation) of 14 cognitive assessments covering 4 domains (executive; working memory, attention and processing speed; episodic learning and memory; visuoperceptual and visuospatial) obtained in 30 healthy controls and 60 RRMS patients.

	Healthy controls	RRMS patients	*t*-value;*p*-Value
Executive			
Letter fluency	0.86(1.10)	0.12(1.12)	−2.26;0.02*
Category fluency	1.22(0.86)	0.88(0.93)	−0.86;0.39
Category switch	0.58(0.68)	0.50(0.93)	0.1;0.91
Stroop color-word interference	0.56(0.70)	−0.08(1.10)	−2.38;0.01*
Working memory, attention and processing speed			
Stroop color naming	−0.08(0.81)	−0.34 (0.97)	−0.66;0.51
Stroop color word reading	−0.07(0.92)	−0.31 (0.95)	−0.47;0.64
PASAT	−0.22(1.06)	−0.56(1.21)	−0.79;0.43
SDMT	0.29(1.04)	−0.11(0.93)	−1.25;0.21
Episodic learning and memory			
BVMT, learning	0.73(0.79)	0.29(1.07)	−1.37;0.17
BVMT, delayed	0.16(0.94)	0.51(1.02)	2.06;0.05*
CVLT, learning	1.40(1.23)	0.85(1.30)	−1.38;0.17
CVLT, delayed	0.57(0.59)	0.05(0.90)	−2.40;0.02*
Visuoperceptual and visuospatial			
Judgment of line orientation	0.58(0.76)	0.43(0.64)	−0.30;0.77
Rey complex figure test copy	−0.06(0.74)	−0.40 (0.94)	−1.28;0.21

Raw test scores were converted to *z*-scores on the basis of age and sex-adjusted normative data for each test. The difference between the RRMS and control groups for each neuropsychological test was assessed using analysis of covariance, covarying for premorbid-IQ (WTAR) (87 degrees of freedom).
PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modality Test; BVMT: Brief Visual Memory Test; CVLT: California Verbal Learning test.
* Indicates significant *p* Values ($p \leq 0.05$).

performance on only four measures (BVMT and CVLT delayed, Stroop color-word interference and letter fluency; Table 2). Inclusion of BDI as a covariate did not change these findings.

Confirmation that only modest cognitive change was evident in our RRMS group was that only 13 of the 60 patients reached the criteria for MCI. Two of the MCI patients were impaired in executive function, 5 in working memory, attention and processing speed domain and 2 in episodic learning and memory domain. Two MCI patients were impaired in the domain of working memory, attention and processing speed, and in episodic learning and memory; the last 2 were impaired working memory, attention and processing speed, and in executive function.

3.3. Group difference in MRI metrics

3.3.1. MRI volumetric measurements

The RRMS patients showed significantly reduced volume in global WM (−1.4%), hippocampus (−0.4 ml), putamen (−0.7 ml) and particularly the thalamus (−2.7 ml) (Table 3).

3.3.2. MRI diffusion tensor imaging

In RRMS patients, there was significantly decreased FA in global WM, and increased MD in global WM and GM. No diffusion abnormalities were detected in deep GM nuclei (see Supplementary Table 1).

3.3.3. MRI perfusion

There was no group difference in perfusion measurements in any deep GM region and global GM and WM (see Supplementary Table 1).

Table 3
Volumetric MRI measurements for global white matter (WM), grey matter (GM) and deep GM nuclei (thalamus, hippocampus, putamen, caudate nucleus and globus pallidum) for the 30 heathy controls and 60 relapsing-remitting (RRMS) patients. The difference between the RRMS and control groups for global WM and GM and deep GM volumes was assessed using ANCOVA with age, gender and premorbid-IQ (WTAR) as covariates (85 degrees of freedom).

	Healthy controls	**RRMS patients**	***t*-value;*p*-Value**
Volumetric MRI measurements			
Mean lesion load, mL (SD)	–	14.6(22.0)	–
Mean normalised brain volume, mL (SD)	1446.6 (142.8)	1392.8 (134.4)	−1.04;0.17
Mean GM volume, % (SD)	45.9(2.1)	45.8(2.9)	0.59;0.56
Mean WM volume, % (SD)	38.7(1.5)	37.3(1.7)	−3.57; < 0.01*
Mean normalised deep GM volume, mL (SD)			
Thalamus	12.9(0.9)	10.2(1.0)	−4.37; < 0.01*
Hippocampus	5.4(0.5)	5.0(0.5)	−3.52; < 0.01*
Putamen	7.2(0.6)	6.5(0.7)	−3.20; < 0.01*
Caudate nucleus	4.8(0.5)	4.5(0.5)	−1.37;0.17
Globus Pallidum	2.4(0.2)	2.3(0.2)	−1.63;0.11

WM: white matter; GM: grey matter.
* Indicates significant *p* Values ($p \leq 0.01$).

3.4. Relationship between deep GM volumes and cognition in RRMS patients

Visual inspection of the quantile plots of the residuals confirmed the normality of the residuals in the regression analyses. Non-constant variance test was not rejected, validating homoskedasticity, and multicollinearity of predictors was satisfactory (variation inflation factor was found to be less than 3.3). Disease duration and Beck depression inventory (BDI-II) did not have significant associations in the regression models. See Supplementary Table 2 for the final results of the multiple regression analysis of the associations between deep GM metrics and neuropsychological assessments, using premorbid IQ (WTAR) as a covariate.

3.4.1. Thalamus and cognition

Thalamic volume was significantly associated with performance on one or more tests in all 4 cognitive domains: (i) executive function (letter fluency), (ii) working memory, attention and processing speed (PASAT, SDMT), (iii) learning and memory (CVLT learning) and (iv) visuoperceptual and visuospatial function (Rey figure copy) (Table 4). After Bonferroni correction, the association between thalamic volume and PASAT, SDMT, and Rey figure copy tests remained significant. These associations remained significant after controlling for WTAR in the regression analysis (Supplementary Table 2).

3.4.2. Hippocampus and cognition

Hippocampus volume was associated with performance on (i) working memory, attention and processing speed (PASAT and SDMT) and (ii) visuoperceptual and visuospatial function (Rey Complex figure copy) (Table 4). After Bonferroni correction, only the association between hippocampus volume and SDMT test remained significant. Similarly, only this association remained after controlling for WTAR in the multiple regression (Supplementary Table 2).

3.4.3. Putamen and cognition

Putamen volume was associated with performance in two domains: (i) executive function (category switching), and (ii) working

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Table 4
Correlation between deep GM volume (thalamus, hippocampus and putamen) and cognition using Pearson product moment correlation coefficient (r).

Domains	Cognitive assessments	Thalamus volume	Hippocampus volume	Putamen volume
Executive	Letter fluency	0.28*	0.11	0.16
	Category fluency	0.22	0.10	0.08
	Category switching	0.24	0.16	0.33**1
	Stroop colour-word interference	0.17	0.03	0.25
Working memory, attention and processing speed	Stroop color naming	0.21	0.03	0.30*
	Stroop color word reading	0.22	0.01	0.27*
	PASAT	0.47***1	0.24*	0.38***1
	SDMT	0.37***1	0.37***1	0.37***1
Episodic learning and memory	BVMT, learning	0.23	0.11	0.10
	BVMT, delayed	0.25	0.09	0.14
	CVLT, learning	0.26*	0.12	0.08
	CVLT, delayed	0.21	0.21	0.21
Visuoperceptual and visuospatial	Judgment of line orientation	0.16	0.13	0.01
	Rey complex figure test copy	0.41***1	0.26*	0.21

PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modality Test; BVMT: Brief Visual Memory Test, CVLT: California Verbal Learning test. Raw test scores were converted to z-scores on the basis of age and gender-adjusted normative data for each test.

* $p \leq 0.05$.
** $p \leq 0.01$.
*** $p \leq 0.001$.
[1] Still significant ($p \leq 0.05$) after Bonferroni correction.

memory, attention and processing speed (PASAT, SDMT, Stroop colour and word reading) (Table 4). After Bonferroni correction, the association between putamen volume and category switching, PASAT, and SDMT tests remained significant. Associations between putamen volume and Stroop colour reading, PASAT, SDMT and category switching were evident in the multiple regression (Supplementary Table 2).

3.5. Relationship between deep GM volume and T2 lesion load

Increased T2 lesion load was associated with decreased volume in WM ($r=-0.28$, $p \leq 0.05$), thalamus ($r=-0.39$, $p \leq 0.01$) and putamen ($r=-0.28$, $p \leq 0.05$). After Bonferroni correction, the association between thalamus volume and T2 lesion load remained significant (Table 5).

4. Discussion

This is the first study we are aware of to simultaneously investigate volume, perfusion and diffusion measurements in deep GM nuclei and perform detailed cognitive assessments in RRMS, thereby enabling a robust investigation of the relationship of cognition with regional deep GM abnormalities. We identified atrophy in the thalamus, hippocampus and putamen and associations between deep GM atrophy in these structures with impaired cognitive function, particularly information processing speed (SDMT and PASAT). Our imaging measures of deep GM volume and diffusion in healthy controls are similar to those reported in the literature (Assaf et al., 2003; Schoonheim et al., 2012, 2015; Hannoun et al., 2012; Benedict et al., 2013), and support the utility of these deep GM metrics to study MS. In addition, we found an absence of diffusion and perfusion abnormalities. To our knowledge, our study is the first to report perfusion measurements using p-CASL in a priori defined deep GM structures, and the findings could be a useful reference for future p-CASL studies.

Table 5
Correlation between deep GM volume (thalamus, hippocampus and putamen) and T2 lesion load using Pearson product–moment correlation coefficient (r) in the 60 RRMS patients.

	WM volume	Thalamus volume	Hippocampus volume	Putamen volume
T2 lesion load	−0.28*	−0.39**,1	−0.18	−0.28*

WM: white matter.

* $p \leq 0.05$.
** $p \leq 0.01$.
[1] Indicates significant p Values ($p \leq 0.05$) after Bonferroni correction.

Although reduced scores in memory (BVMT and CVLT delayed) and executive functions (Stroop interference and letter fluency test) were found when compared with healthy controls, the overall average scores on these tests indicate intact cognitive function in the majority of this RRMS cohort. The main novelty of this work was to have recruited an exclusively RRMS cohort, rather than a mixed-type MS group (Houtchens et al., 2007; Mesaros et al., 2012; Schoonheim et al., 2015) and generally preserved cognitive function (vs. Schoonheim et al., 2012), in addition to having simultaneous multi-modal MRI metrics (volume, diffusion and perfusion) in several deep GM structures.

Volumetric and DT imaging enabled us to investigate atrophy and brain micro-structural properties respectively. The DTI abnormalities (increased MD and decreased FA) seen in the global WM of our MS cohort patients are consistent with heterogeneous pathology, including axonal loss, demyelination, edema and gliosis that in turn could also account for the detected WM atrophy (−1.4% in this group of RRMS patients relative to healthy controls). A greater extent of WM atrophy (−4.9%) was reported by Chard et al. (2002) in early RRMS patients with a mean disease duration of 1.8 years. This difference suggests that our cohort of RRMS patients, with RRMS remaining longer term (mean disease duration of 5.1 years ranging from 1 to 15 years), were experiencing a milder disease course and minimal neurological and neuropsychological impairments. While the absence of atrophy in the whole GM would suggest generally intact cortical structures, our findings do not exclude the possibility that there were areas of regional cortical grey matter atrophy. Also, the higher MD in the global GM, as in other studies (Akbar et al., 2010), indicates altered micro-structural properties in the GM in our RRMS group.

Atrophy in the thalamus, hippocampus and putamen could result from focal demyelinated lesions, diffuse oxidative injury and neurodegeneration, all of which have been observed in the deep GM of MS patients (Haider et al., 2014). Although perhaps more likely in MS patients with long-standing disease, histopathologically

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confirmed neurodegeneration (axonal and neuronal loss) may be a driver for MRI-measured cortical atrophy (Popescu et al., 2015). The RRMS cohort used in the current study adds to a growing literature that thalamic atrophy is an especially prominent and early site of deep GM decline in MS (Minagar et al., 2013). Consistent with the current study, Schooheim et al. (2015) reported that only patients with severe cognitive impairment had altered thalamic diffusion properties (decreased FA and increased MD). Lastly, the intact global GM tissue volume might suggest a more favourable type of disease course in our cohort of RRMS patients, although much longer follow up will be needed to determine whether this is the case. Similarly, longitudinal follow up may determine the relative clinical value of reduced thalamic volume as a potential MRI predictor of response to treatments (Simon et al., 2014).

The hypothesis that anatomically distant WM lesions, through anterograde and retrograde (Wallerian) axonal degeneration and loss, also contribute to deep GM abnormalities (Muhlau et al., 2013) is supported by the current study. We found a significant association between WM lesion load and both thalamus and putamen volume.

Decreased cortical and subcortical perfusion has been detected in previous studies in MS (Inglese et al., 2007, 2008; Varga et al., 2009; Debernard et al., 2014; Francis et al., 2013). In a former study of 25 RRMS patients of short disease duration less than 5 years (mean 2.4 years), we detected reduced GM perfusion, in the absence of GM atrophy (Debernard et al., 2014). However, a decrease in global GM perfusion was no longer evident in the present cohort (see Supplementary Table 1) of 60 patients (which included the 25 early RRMS patients previously reported). One reason for this difference could be that the longer disease duration and lower disability levels of most of the RRMS subjects reflected an overall more “benign” RRMS disease course in the current sample. Absence of hypoperfusion in GM structures in more established RRMS patients was also reported by Rashid et al. (2004). Their patients had a relatively long disease duration (mean disease duration of 10 years), and a low disability (median EDSS 2.5), also indicating a generally favorable disease course. By contrast, cortical and subcortical hypoperfusion was reported in a group of cognitively impaired patients with secondary progressive MS, compared with non-impaired patients (Francis et al., 2013). Collectively, these perfusion findings suggest that 1) structural changes (neuronal loss and microstructural abnormalities) are occurring independently of perfusion abnormalities (implying metabolic dysfunction) in deep GM; 2) neuronal metabolic dysfunction (reflected by reduced perfusion) occurs at different levels during the course of RRMS, being more pronounced in the early years, and less evident with longer disease duration; and/or 3) perfusion abnormalities rely on the level of cognitive deficit experienced by MS patients. These alternatives require more detailed investigation and longitudinal follow-up of patients converting to more severe disability and cognitive impairment.

White matter demyelination contributes to disruption in WM tracts across multiple brain networks, causing the slowing of information transmission speed (Dineen et al., 2009). Our results confirm the significant association of thalamus and putamen atrophy with MS-related information processing speed slowing (as measured by SDMT and PASAT). Hippocampal atrophy may also contribute to the diverse skills, such as memory and/or information processing speed/attention, required for high scores on the SDMT test. Our findings support earlier work (Batista et al., 2012). That study, however, investigated 85 mixed-type MS patients exhibiting impaired attention and cortical and subcortical atrophy, whereas our study revealed associations between deep GM atrophy and cognitive performance in a restricted group of RRMS patients who showed relatively preserved cognitive function and no global cortical atrophy.

The association between thalamic volume and cognition reflects the role of the thalamus in the control of cortical information processing and cognition (Saalmann, 2014). With respect to the putamen, as part of striatum, this structure receives inputs from prefrontal cortex, particularly from dorsolateral prefrontal cortex, highly implicated in executive functions and working memory, and from the orbitofrontal cortex which is known to be involved in decision making and reward-seeking behavior (Tziortzi et al., 2014). These connections are likely to account for the associations between the putamen volume with executive function, working memory, attention and processing speed. Additionally, putamen receives input from the frontal eye fields that can account for theses associations too, especially when performance depends on visual searching (Batista et al., 2012).

The present study has limitations. Analysis of MRI metrics (volume, perfusion and diffusion) was performed in GM. However, we did not include specific MRI sequences such as double inversion recovery (DIR) to identify cortical or deep GM lesions. Hence, GM investigated here may have reflected clearly lesioned on DIR but normal appearing on more conventional sequences, normal appearing but masked underlying pathophysiology, although the sensitivity of this marker is relative low (Minagar et al., 2013), or normal appearing without underlying pathology. Limitations are inherent from the choice of MRI sequences and methodologies used in this study. Conventional DTI-derived measurements from model tensor imaging assume normal distribution in diffusion, which may not be appropriate in GM in MS. More advanced diffusion models may be useful when assessing GM diffusion changes in MS, such as Diffusion Orientational Complexity (DOC) model derived from diffusion imaging (Muhlert et al., 2015) or non-Gaussian diffusion imaging (Bester et al., 2015).

In conclusion, we have found prominent deep GM atrophy of thalamus, hippocampus and putamen in RRMS patients. This atrophy is associated with cognitive performance. Future research needs to improve our understanding on the mechanisms of deep GM atrophy in RRMS, and to elucidate the relationship between deep GM atrophy and the evolving cognitive and neurological status of people with MS.

Contributors

LD, TRM, DHM and DFM conceptualized the research and contributed to the study methods and analyses. JE and DFM performed RRMS patient’s selection and neurological assessments. SVS, CG, JRO, JCDA designed and performed the behavioral experiments. LD performed brain analysis. LD and SA performed statistical analysis. LD and DHM wrote the manuscript. All authors have made substantial contributions to all of the following: (1) revising the article critically for important intellectual content and (2) final approval of the version to be submitted. Moreover, each of the authors has read and concurs with the content of the present manuscript.

Conflict of interest

No conflict of interest was disclosed.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2015.10.004.

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