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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