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Review

Localized grey matter atrophy in multiple sclerosis: A meta-analysis of voxel-based morphometry studies and associations with functional disability

J. Lansley[a,*], D. Mataix-Cols[b], M. Grau[b], J. Radua[b,c], J. Sastre-Garriga[d]

[a] Radiology Academy, Norfolk and Norwich University Hospital, NR4 7UB, United Kingdom
[b] Institute of Psychiatry, King's College London, De Crespigny Park, London, SE5 8AF, United Kingdom
[c] Research Unit, FIDMAG – CIBERSAM, Sant Boi de Llobregat, Barcelona, Spain
[d] Department of Neurology/Neuroimmunology and Multiple Sclerosis Centre of Catalonia (Cemcat), Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

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ABSTRACT

Grey matter (GM) damage in Multiple Sclerosis (MS) occurs largely independent of white matter (WM) lesions and shows stronger correlation with clinical parameters than WM damage but no clear pattern of GM atrophy distribution has emerged in the literature. We used Signed Differential Mapping (SDM), a novel neuroimaging meta-analytical method, to assess global and regional GM volume differences in MS. Meta-regression methods were used to explore potential effects of disease duration and degree of functional disability. We found a highly localized pattern of regional GM volume loss in Relapsing Remitting MS involving bilateral thalamus, basal ganglia structures, pre/postcentral regions and cingulate gyrus. These results remained largely unchanged after subgroup and sensitivity analyses. Furthermore, GM volume loss in left pre/postcentral regions correlated with increasing functional disability in MS. These results demonstrate that GM atrophy occurs as a regional rather than global process in MS, and that functional disability is specifically associated with atrophy of the left pre/post central gyrus. Further investigation is needed to determine whether these structures are targeted by neurodegenerative processes and to establish their clinical and neurocognitive correlates.

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* Corresponding author at: Norwich Radiology Academy, The Cotman Centre, Colney Lane, Norwich, Norfolk, NR4 7UB, United Kingdom. Tel.: +44 0 7811340021.
E-mail address: Dr.Joseph.Lansley@gmail.com (J. Lansley).

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1. Introduction

Grey matter (GM) damage in MS was first reported by Sander in the 19th century (Sander, 1898). Early histopathological techniques underestimated the extent of cortical change in MS. Consequently, research focussed on more conspicuous white matter (WM) inflammatory demyelination (Hulst and Geurts, 2011). Only relatively recently has the true extent of GM demyelination been appreciated. Bo et al. (2003) used myelin immunohistochemistry to demonstrate that an average of 26.5% of the cortex was involved by GM demyelination in a sample of 20 MS patients. Contrary to previous studies which reported a predominance of juxtacortical GM lesions (Brownell and Hughes, 1962; Kidd et al., 1999), the main pattern of cortical involvement was subpial demyelination, often extending over multiple gyri and accounting for over two thirds of the total cortical lesion burden. A subsequent study correlating histopathological findings with MRI demonstrated that these extensive subpial lesions were not visible on MR imaging or standard luxol fast blue histochemistry, explaining underestimation by previous histological and imaging studies alike. Cortical demyelination appeared to be largely independent of focal or diffuse WM abnormalities, suggesting that GM changes could represent a distinct pathological process in MS (Bo et al., 2007).

In vivo assessment of demyelination by MRI has been used in research as a measure of disease activity and as a correlate for histopathological studies. Fluid attenuated inversion recovery (FLAIR) sequences and intravenous contrast have improved lesion detection although GM involvement remains largely undetected (Hulst and Geurts, 2011). Double inversion recovery (DIR) sequences improve detection of GM changes but are not yet widely used in clinical practice which remains focused exclusively on WM/juxtacortical changes (Polman et al., 2011).

Structural neuroimaging studies have shown GM atrophy, assessed by automated segmentation approaches, to be a highly reproducible measure of the neurodegenerative component of MS (Miller et al., 2002). GM atrophy appears to be associated with clinical factors such as physical disability, cognitive decline and disease duration (DD) (Amato et al., 2007; Benedict et al., 2004; Calabrese et al., 2007, 2010; Chen et al., 2004; De Stefano et al., 2003; Fisher et al., 2008; Fisniku et al., 2008; Pagani et al., 2005; Roosendaal et al., 2011; Rudick et al., 2009; Sailer et al., 2003; Sastre-Garriga et al., 2005a, 2004; Tedeschi et al., 2005). Relative sparing of the cortex has been reported in patients with benign MS (BMS) (Calabrese et al., 2009), and measures of GM atrophy have shown both independence from WM changes and a stronger correlation with clinical parameters than WM damage (Benedict et al., 2004; Bo et al., 2007; Calabrese et al., 2007; De Stefano et al., 2003; Fisher et al., 2008; Fisniku et al., 2008; Roosendaal et al., 2011; Sastre-Garriga et al., 2005a; Tedeschi et al., 2005). Recently studies utilising magnetic transfer ratio (MTR), MR spectroscopy and diffusion tractography have revealed abnormalities in the structure of normal appearing WM and GM which may also contribute to functional impairment in MS (Filippi et al., 2012; Sastre-Garriga et al., 2005b). The inconspicuous nature of clinically significant changes on standard neuroimaging may help explain the clinico-radiological paradox in MS (Barkhof, 2002).

Whilst GM changes have shown clinico-radiological correlation, it is unclear whether GM volume loss occurs as a diffuse, global process or as more focal degeneration with regional predominance. Regional atrophy in MS could help explain clinical characteristics of the disease and provide an empirical basis for sub-categorisation of this heterogeneous disorder. Establishing a clinically significant pattern of GM involvement in MS, and MS subtypes, could also offer benefits for diagnosis and treatment.

Fully automated, whole-brain voxel-based morphometry (VBM) methods utilising standard 3D T1 sequences provide a powerful tool to study the neural substrates of neurological and psychiatric disorders. A modified method of VBM, which "masks" WM lesions to avoid their misclassification as GM in the segmentation step, is commonly used in MS research. Using these techniques GM losses have been reported in multiple cortical and subcortical regions (Audoin et al., 2006, 2010; Battaglini et al., 2009; Bendfeldt et al., 2010, 2012, 2009; Bodini et al., 2009; Ceccarelli et al., 2012, 2008a,b; Duan et al., 2012; Henry et al., 2008; Khaleeli et al., 2007; Mesaros et al., 2008a,b; Morgen et al., 2006; Prakash et al., 2010; Prinster et al., 2010, 2006; Raz et al., 2010a,b; Riccitelli et al., 2011a,b, 2012; Senda et al., 2012; Sepulcre et al., 2006; Spanò et al., 2010; Wybrecht et al., 2012); however a coherent pattern of disease has not emerged. Even the most frequently reported findings have been inconsistent, for example thalamic atrophy was been reported in CIS patients by Audoin et al. (2010) and Henry et al. (2008), whilst no significant differences were found by Raz et al. (2010a) and Ceccarelli et al. (2008a).

Inconsistent findings of regional GM atrophy could be attributed to a number of methodological issues. Small sample sizes, common in VBM studies, may lack the power to detect subtle differences between groups, especially in the early course of the disease. Categorical, phenotypical classifications of MS subtypes are widely used in research but as yet have no proven pathophysiological basis and could be a potential source of bias. In addition, subpial demyelination, the most prevalent pattern of atrophy in MS, is poorly demonstrated by routine T1 sequences used in VBM which could therefore underestimate the true extent of degenerative changes in MS.

Recently developed meta-analytic methods have been successfully applied to VBM studies in a number of neurological and psychiatric disorders allowing the identification of the most prominent and replicable findings from published and unpublished data (Ferreira et al., 2011; Li et al., 2012; Nakao et al., 2011; Pan et al., 2012; Radua and Mataix-Cols, 2009). No such study has been conducted on VBM findings in MS. The aim of this study was threefold: to establish whether GM atrophy shows significant regional predominance in MS, to determine the most prominent and replicable GM structural abnormalities in MS, and to correlate

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