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Semi-automatic brain region extraction (SABRE) reveals superior cortical and deep gray matter atrophy in MS

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In multiple sclerosis (MS), atrophy occurs in various cortical and subcortical regions. However, it is unclear whether this is mostly due to gray (GM) or white matter (WM) loss. Recently, a new semi-automatic brain region extraction (SABRE) technique was developed to quantify parenchyma volume in 13 hemispheric regions. This study utilized SABRE and tissue segmentation to examine whether regional brain atrophy in MS is mostly due to GM or WM loss, correlated with disease duration, and moderated by disease course. We studied 68 MS patients and 39 normal controls with 1.5 T brain MRI. As expected, MS diagnosis was associated with significantly lower ($P < 0.001$) regional brain parenchymal fractions (RBPFs). While significant findings emerged in 11 GM comparisons, only four WM comparisons were significant. The largest mean RBPF percent differences between groups (MS < NC) were in the posterior basal ganglia/thalamus region (−19.3%), superior frontal (−15.7%), and superior parietal (−14.3%) regions. Logistic regression analyses showed GM regions were more predictive of MS diagnosis than WM regions. Eight GM RBPFs were significantly correlated ($P < 0.001$) with disease duration compared to only one WM region. Significant trends emerged for differences in GM, but not WM between secondary progressive (SP) and relapsing–remitting MS patients. Percent differences in GM between the two groups were largest in superior frontal (−9.9%), medial superior frontal (−6.5%), and superior parietal (−6.1%) regions, with SP patients having lower volumes. Overall, atrophy in MS is diffuse and mostly related to GM loss particularly in deep GM and superior frontal–parietal regions.

Keywords: Multiple sclerosis; Regional brain atrophy; Quantified magnetic resonance imaging; Gray matter

Introduction

Multiple sclerosis (MS) is a demyelinating and degenerative disease of the central nervous system (CNS) characterized by lesion formation and atrophy of the brain and spinal cord. Brain lesions were described in a series of apparent MS cases by Cruveilhier (1835), and atrophy was later documented by Charcot (1877). Subsequent autopsy studies revealed ventriculomegaly in a significant number of MS patients (Barnard and Triggs, 1974; Brownell and Hughes, 1962; Friedman and Davidson, 1945). With advances in neuroimaging technology, it is now well established that brain atrophy occurs in approximately 50% of MS patients studied in vivo (Chard et al., 2002b; Kassubek et al., 2003; Miller et al., 2002; Pelletier et al., 2003; Zivadinov and Bakshi, 2004). Atrophy of gray (GM) and white matter (WM) occurs early in the disease (Chard et al., 2002b; Chen et al., 2004; Ge et al., 2001; Quarantelli et al., 2003), increases with disease progression, and reflects widespread loss of myelin, axons, glial cells, and neuronal cell bodies (Minagar et al., 2004; Pelletier et al., 2004; Silber and Sharief, 1999). It is likely that clinical impairment results once brain atrophy reaches a critical threshold (Zivadinov et al., 2004a), making this an important variable to measure.

Few studies have compared measurements of WM and GM atrophy in MS. Chard et al. (2002b) found greater WM than GM atrophy in early relapsing–remitting (RR) disease, although lesion load correlated only with GM loss. In another recent study (Ge et al., 2001), RR patients had more WM atrophy than controls but the same GM volume. These authors reported a significant correlation between total lesion volume and WM but not GM volume. Conversely, a more recent study with 50 RR patients found lower GM, but not WM volume, when compared to normal controls (Quarantelli et al., 2003). In this study, it was also found that total lesion volume was associated with GM but not WM loss. It has been demonstrated that over a 3-year period, patients converting to clinically definite MS were those who also developed significant GM but not WM atrophy (Dalton et al., 2004).

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Recently, another study showed increasing GM, but not WM atrophy, over 2 years in the early stage of relapsing–remitting (RR) MS (Tiberio et al., 2005). Discrepancies among these studies may be explained by differences in tissue segmentation methodology, heterogeneity in the rate of volume loss, and differences in the pathogenesis of atrophy between the two tissue compartments.

Regional brain atrophy is a topic of increasing interest in the literature. Rates of volume change may differ across brain regions, and pathology in specific regions may be more predictive of clinical phenomena than whole brain measures (Benedict et al., 2002; Feinstein et al., 2004). Manual tracings of lobes or structures (Allen et al., 2002; Tzourio-Mazoyer et al., 2002) have been pursued, but these methods are time-intensive and prone to poor reproducibility because of inter-individual neuroanatomical variation. To increase reliability, Zivadinov et al. (2003) used a digital 3D version of the *Harvard Medical School Whole Brain Atlas* as a reference to manually segment the frontal lobes and pons. Normalized regional brain parenchymal fractions (RBPFs) correlated better with MRI-defined brain lesions than absolute measures of regional brain volume (Locatelli et al., 2004; Zivadinov et al., 2003). This method was recently extended to all four lobes (Benedict et al., 2005). Regional lobar atrophy accounted for more variance than lesion burden and whole brain atrophy in predicting MS-associated memory dysfunction. An automated method was recently developed that involves warping a pre-labeled neuroanatomical atlas to individual patient data (Meier and Fisher, 2005). This method combined co-registration of standard space (Harvard Brain Atlas) and target images, with landmark identification (lateral ventricles, outer brain surface, inter-hemispheric surface). The authors reported good scan–rescan reliability and minimal error across eight regions in MS brains.

Voxel-based morphometry (VBM), a registration-based method, is a potentially useful technique for regional brain atrophy measurement. VBM can measure parenchyma volume in multiple regions, the size of which can be specified by the user. In this approach, the brain is spatially normalized to a template with smoothing to provide optimal fit. Once the image data are 'normalized,' differences in tissue composition can be assessed voxel by voxel (Pagani et al., 2005). The result is a statistical parametric map that highlights regions where GM concentrations, for example, may differ between groups. A caveat of VBM is that detection decreases for regions with greater neuroanatomical variability (Quarantelli et al., 2002; Tisserand et al., 2002), a problem which is apt to be prominent in populations with brain atrophy. In other words, this method may be subject to considerable within-subject error when an atrophied brain is modified to conform to 'normal' template.

To avoid the methodological difficulties discussed above, the present study utilized a recently published (Dade et al., 2004) procedure called semi-automatic brain region extraction (SABRE). Unlike previously described measures that involve warping subject's brain to standardized space, like Meier and Fisher's (2005) approach, SABRE adjusts the template to the subject's brain. That is, an individualized Talairach brain map is created for each subject and used to delineate 13 regions in each hemisphere, based on standard landmarks and their connections. In the initial study (Dade et al., 2004), inter-rater reliability was high for all volumes, with coefficients between 0.91 and 0.99. These authors also found that older normal adults had lower GM and WM volumes than younger adults in the majority of brain regions. Feinstein et al. (2004) employed SABRE to show that MS patients with major depressive disorder had significantly less GM volume in the left anterior temporal region compared to normal controls.

In the present study, we combined SABRE with a tissue segmentation technique to measure regional brain atrophy as reflected by both GM and WM tissue loss. Based on our previous work (Benedict et al., 2002, 2004; Bermel et al., 2003), we predicted that atrophy would be most distinct in superior frontal/parietal lobes and deep gray matter. We also tested the hypothesis that GM atrophy is more prominent in MS than WM atrophy.

Materials and methods

Participants

We studied sixty-eight MS patients. Inclusion criteria were as follows: clinically definite MS (McDonald et al., 2001), age 18–70 years, EDSS < 8.5. Exclusion criteria were relapse or steroid treatment in the 3 months preceding the study, pre-existing medical condition known to be associated with brain atrophy (neurodegenerative disorder, cerebrovascular disease, positive history of alcohol abuse, etc.). Thirty-one patients had relapsing–remitting (RR) disease, and the remainder had secondary progressive (SP) course as defined by consensus classification procedures (Lublin et al., 1996). Sixty-seven patients underwent quantified neurological examination and Expanded Disability Status Scale (EDSS) evaluation (Kurtzke, 1983).

Thirty-nine healthy volunteers served as normal controls (NC). One-way ANOVA showed that MS and NC groups significantly differed slightly on age ($F_{1,106} = 8.1$, $P < 0.01$). The proportion of males and females did not differ across groups by Chi-square test ($\chi^2 = 2.1$, $P = 0.14$) nor did the proportion of Caucasians and African-Americans ($\chi^2 = 3.7$, $P = 0.15$). NC subjects with pre-existing medical history or conditions known to be associated with brain atrophy and/or those who presented hyperintense brain abnormalities on T2-weighted images were excluded from the study. Table 1 also shows demographic information by MS group. One-way ANOVA naturally showed that RR and SP groups significantly differed on age ($F_{1,67} = 4.5$, $P < 0.05$) and disease duration ($F_{1,67} = 8.1$, $P < 0.01$). The proportion of males and females did not differ across groups by Chi-square test ($\chi^2 = 0.05$, $P = 0.82$) nor did the proportion of Caucasians and African-Americans ($\chi^2 = 0.73$, $P = 0.39$).

Table 1
Demographics for MS patients and controls

	MS (all) $n = 68$	RRMS $n = 37$	SPMS $n = 31$	NC $n = 39$
Mean age (years) ± SD	45.3 ± 9.7	43 ± 10.2	47.9 ± 8.4	39.4 ± 11.5
% Caucasian	95	92	97	87
% female	79	78	81	67
Mean disease duration (years) ± SD	13.5 ± 9.6	10.6 ± 7.3	16.9 ± 10.8	–
Median EDSS	1.5	1.5	4.0	–

Note. MS = multiple sclerosis; RRMS = relapsing–remitting MS; SPMS = secondary progressive MS; NC = normal control; SD = standard deviation; EDSS = Expanded Disability Status Scale.