

# The thalamus and multiple sclerosis

## Modern views on pathologic, imaging, and clinical aspects

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### ABSTRACT

The paired thalamic nuclei are gray matter (GM) structures on both sides of the third ventricle that play major roles in cortical activation, relaying sensory information to the higher cortical centers that influence cognition. Multiple sclerosis (MS) is an immune-mediated disease of the human CNS that affects both the white matter (WM) and GM. A number of clinical observations as well as recent neuropathologic and neuroimaging studies have clearly demonstrated extensive involvement of the thalamus, basal ganglia, and neocortex in patients with MS. Modern MRI techniques permit visualization of GM lesions and measurement of atrophy. These contemporary methods have fundamentally altered our understanding of the pathophysiologic nature of MS. Evidence confirms the contention that GM injury can be detected in the earliest phases of MS, and that iron deposition and atrophy of deep gray nuclei are closely related to the magnitude of inflammation. Extensive involvement of GM, and particularly of the thalamus, is associated with a wide range of clinical manifestations including cognitive decline, motor deficits, fatigue, painful syndromes, and ocular motility disturbances in patients with MS. In this review, we characterize the neuropathologic, neuroimaging, and clinical features of thalamic involvement in MS. Further, we underscore the contention that neuropathologic and neuroimaging correlative investigations of thalamic derangements in MS may elucidate not heretofore considered pathobiological underpinnings germane to understanding the ontogeny, magnitude, and progression of the disease process. *Neurology*® 2013;80:210-219

### GLOSSARY

**CIS** = clinically isolated inflammatory demyelinating syndrome; **DIR** = double inversion recovery; **DTI** = diffusion tensor imaging; **EDSS** = Expanded Disability Status Scale; **GM** = gray matter; **LGN** = lateral geniculate nucleus; **MS** = multiple sclerosis; **NAGM** = normal-appearing gray matter; **NAWM** = normal-appearing white matter; **SWI** = susceptibility-weighted imaging; **WM** = white matter.

Multiple sclerosis (MS) is a progressive inflammatory and degenerative disease of the human CNS that leads to demyelination and neuronal/axonal loss. Both the etiology and cure for MS remain elusive, and for many years scientific research into the pathogenesis of MS has heavily focused on a disease principally affecting CNS white matter (WM).

Notwithstanding the traditional focus upon WM as the predominant target of the disease mechanisms in MS, recent findings, which indicate significant gray matter (GM) involvement, are an important and substantial refinement in our understanding of the pathobiological underpinnings of the disease process in MS, of particular relevance to cognitive decline as well as overall disease worsening.<sup>1,2</sup> Neuropathologic data implicate significant cortical demyelination and neuro-axonal and synaptic loss in both the early and late phases of the disease process.<sup>2-5</sup> Both cortical<sup>3</sup> and subcortical demyelination are observed during the course of MS, targeting a landscape of GM-rich structures including the thalamus, hippocampus, caudate, putamen, globus pallidus, and other structures of the basal ganglia.<sup>5,6</sup>

Both postmortem and in vivo studies have revealed extensive MS lesions of the GM structures.<sup>1,7,8</sup> In general, the neuropathologic features of GM involvement in MS differ significantly

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from WM lesions.<sup>5</sup> For example, certain features such as lymphocyte infiltration, complement deposition, and disruption of the blood–brain barrier are typically not detected in the GM of chronic autopsy samples but have been reported in cortical lesions of active MS. More robust and long-lasting neuroinflammation is the dominant component of newly forming WM lesions. Similar to diffuse involvement of the WM in MS, demyelination of the cerebral cortex and cerebellum,<sup>1</sup> deep GM structures,<sup>8,9</sup> and the GM of the spinal cord<sup>10</sup> have been reported, supporting the concept of “diffuse brain involvement” in MS. Pathology within the thalamus is frequently observed in MS, but less well characterized when compared to the delineation of WM compartment lesions.<sup>7,8</sup> As a major portion of the diencephalon in primates, the thalamus serves as a gateway to the cerebral cortex and is heavily involved with its activity. However, its unique structural division into various nuclear complexes enables the thalamus to connect with other subcortical structures. Neuroanatomically, as a “relay organ,” the thalamus is involved in a wide range of neurologic functions including motor, sensory, integrative, and higher cortical functions. Further, the thalamus also plays a significant role in other functions such as the regulation of sleep and wakefulness, memory, emotion, consciousness, awareness, and attention. The thalamus is also involved in ocular motility, posture, and executive function. Location, unique functions, and vulnerability to MS neuropathology from the earliest disease stages<sup>11–14</sup> render the thalamus a critical barometer of diffuse neuropathologic damage in MS. Advanced neuropathologic and neuroimaging methods are slowly emerging, providing us with a better view of the full extent of thalamic abnormalities in patients with MS.

Thalamic axons are well known to transmit information between a number of subcortical and specific cortical areas. As such, damage to the thalamic nuclei and their connections potentially impairs a wide range of neurologic functions that may clinically translate into significant cognitive and mental disability.<sup>15,16</sup> Thalamic pathology in MS accumulates on a background of normal age-related reduction in thalamic volume,<sup>17</sup> which is in itself associated with a decline in cognitive capacity, particularly

mental speed and information processing speed.<sup>18</sup> Predicated on the known role of the thalamus in the normal operation of the human CNS, and based on the growing knowledge of the extent of its damage and involvement in the pathogenesis of MS, we aimed to review and discuss these abnormalities in the context of recently emerging neuropathologic and neuroimaging studies.

**THALAMIC NEUROPATHOLOGY IN MS** The notion that clinically relevant MS pathology is restricted to focal WM lesions has been overwhelmingly negated by an expanding body of neuropathologic data implicating significant cortical myelin, neuro-axonal, and synaptic loss<sup>2–5,9,19</sup> in both early and late stages of the disease. Pathology afflicting the deep GM structures, in particular the thalamus, is frequently observed in MS, but less well studied. Significant neuropathologic and neuroimaging studies addressing thalamic involvement in MS are presented in the table. While informative, these studies are limited by their small sample size, retrospective design, registration biases, and an absence of treatment effects on thalamic MRI-related outcomes over the course of time.

**Distribution.** The extent of subcortical GM demyelination correlates well with the extent of cortical, but not WM, demyelination,<sup>8</sup> although more studies are needed to determine the relationship between the pathologic processes operating in the subcortical GM with respect to those in the WM. Thalamic GM lesions may extend into the surrounding WM; however, a significant proportion of deep gray plaques are in fact confined to the subcortical GM, with edges that are abruptly demarcated in juxtaposition with well-recognized anatomic WM borders.<sup>8,10</sup> Extensive, confluent subependymal GM demyelination is relatively common in the paraventricular nuclei of the thalamus,<sup>10</sup> raising the possibility of a pathogenic factor within the CSF. While this hypothesis is supported by the demonstration of B-cell aggregates in association with the fourth ventricle and its lateral recesses in the experimental allergic encephalomyelitis model of MS,<sup>20</sup> the “follicles” identified in the meninges in topographic association with zones of subpial demyelination in the cortex of some patients with secondary progressive disease<sup>21</sup> have not been identified in association with the ventricular system in humans.

Diffuse microglial activation is detectable in thalamic normal-appearing GM (NAGM),<sup>8</sup> but to a lesser degree than one typically observes in the normal-appearing WM (NAWM) of patients with long-standing disease. Extralesional microglial activation, characterized by thickening of cell processes and upregulation of human leukocyte antigen–DR expression, is a highly sensitive, albeit nonspecific, indicator of CNS pathology. In MS, retrograde and anterograde diffuse axonal injury is the

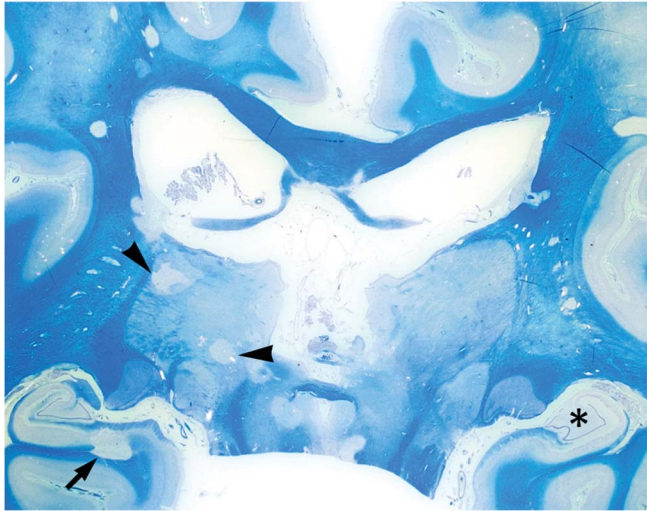
**Table Summary of the most relevant articles on the neuropathologic and neuroimaging findings of thalamic involvement in multiple sclerosis**

| Original article                       | No. of subjects and disease subtype   | Major neuropathologic and neuroimaging findings  |
|--|---|--|
| Cifelli et al. (2002) <sup>7</sup>     | 14 SPMS and 14 controls   | Utilizing MRI, MRS, and postmortem histopathologic studies with focus on thalamic neuronal loss, the authors reported significant neuronal damage in MS.   |
| Wylezinska et al. (2003) <sup>51</sup> | 14 RRMS and 14 controls   | Utilizing structural MRI and MRS studies, the authors assessed thalamic neurodegeneration in patients with RRMS and reported reduction of both NAA concentration and thalamic volume, which indicated a neurodegeneration component in the neuropathology of MS. The authors concluded that the decrease in NAA concentration and thalamic volume suggests that neurodegeneration contributes to the neuropathology of MS in an even earlier stage of the disease.   |
| Vercellino et al. (2005) <sup>9</sup>  | 6 MS (3 RRMS and 3 SPMS)  | The authors performed a neuropathologic examination of MS brains to assess the extent and distribution of GM demyelinating lesions in MS with a focus on neuronal loss and synaptic loss. They reported the presence of demyelinating lesions in the thalamus, cerebral cortex, basal ganglia, and hippocampus. It was concluded that GM demyelination and neuronal loss could contribute to disability and cognitive decline in MS.   |
| Davies et al. (2004) <sup>47</sup>     | 38 RRMS and 35 controls   | Utilizing MTR in patients with early RRMS, the authors reported abnormality of thalamic MTR and thalamic involvement within the first 5 years of MS onset.   |
| Houtchens et al. (2007) <sup>16</sup>  | 79 MS (62 RRMS, 16 SPMS, and 1 PPMS) and 16 controls                                  | Normalized thalamic volume was lower in patients with MS compared to controls, and cognitive performance in all domains was related to thalamic volume in the MS group. A weak correlation between thalamic atrophy and physical disability score was detected. However, cognitive performance in all domains was moderately to strongly related to thalamic volume in patients with MS. The authors concluded that thalamic atrophy was a clinically relevant biomarker of the neurodegenerative disease process in MS. |
| Mesaros et al. (2008) <sup>37</sup>    | 28 pediatric RRMS and 21 controls   | In pediatric patients with MS, different from what occurs in adult patients with MS, GM atrophy appears to affect the thalamus exclusively.  |
| Vercellino et al. (2009) <sup>8</sup>  | 14 MS (7 SPMS, 6 RRMS, and 1 hyperacute MS) and 12 controls (6 normal and 6 with ALS) | Demyelination and neurodegenerative changes are common in MS deep GM and may contribute to clinical deficits.  |
| Ramasamy et al. (2009) <sup>13</sup>   | 71 MS (40 RRMS, 17 PPMS, and 14 SPMS), 17 CIS, and 38 controls                        | This study supported selective deep GM atrophy (mostly thalamic), showed cerebellar WM atrophy from the earliest clinical stages, and showed that cortical thinning advances with disease progression.   |
| Gilmore et al. (2009) <sup>10</sup>    | 14 MS (11 SPMS, 2 PPMS, and 1 RRMS) and 3 controls                                    | The authors reported the presence of significant regional variations in the extent and pattern of GM demyelination in MS.  |
| Henry et al. (2009) <sup>11</sup>      | 24 CIS and 18 controls  | A stepwise regression analysis demonstrated that thalamocortical lesion volume and the mean diffusivity in track regions connecting lesion and thalami were significantly correlated with thalamic volumes in patients, explaining 66% of the variance, a finding not observed in regions outside the thalamocortical WM.  |
| Tovar-Moll et al. (2009) <sup>49</sup> | 24 MS (13 RRMS and 11 SPMS) and 24 controls   | Utilizing DTI at 3 T, the authors assessed thalamic involvement and its impact on clinical disability in patients with MS. They concluded that DTI was able to detect abnormalities in the normal-appearing thalamus of patients with MS and there was an association between thalamic DTI measures and functional impairment in MS.   |
| Rocca et al. (2010) <sup>15</sup>      | 73 relapse-onset MS (20 CIS, 34 RRMS, and 19 SPMS) and 13 controls                    | Utilizing conventional imaging and MTR, the authors detected that thalamic atrophy was correlated with accumulation of disability in patients with MS. In addition, WM lesions were likely to contribute to the thalamic tissue loss observed in patients with MS.   |
| Audoin et al. (2010) <sup>33</sup>     | 62 CIS and 37 controls  | Based on this study which involved patients with CIS, atrophy mainly affected the limbic system and the deep GM (bilateral thalami) at the first stage of MS.  |
| Calabrese et al. (2011) <sup>14</sup>  | 105 CIS and 24 controls   | The study found that selective GM atrophy is relevant in patients with CIS who convert early to MS. The multivariate analysis identified the atrophy of the superior frontal gyrus, thalamus, and cerebellum as independent predictors of conversion to MS.  |
| Mesaros et al. (2011) <sup>48</sup>    | 54 PPMS and 8 controls  | Using conventional and DTI brain scans, the authors assessed thalamic damage in patients with PPMS and concluded that thalamic damage predicts the evolution of PPMS.  |
| Hagemeyer et al. (2012) <sup>41</sup>  | 42 CIS and 65 controls  | Patients with CIS showed significantly increased content and volume of iron, as determined by abnormal SWI-phase measurement in the various SDGM structures, especially in the pulvinar nucleus of thalamus, suggesting that iron deposition may precede structure-specific atrophy.   |
| Batista et al. (2012) <sup>59</sup>    | 86 MS (59 RRMS and 27 SPMS) and 25 controls   | Utilizing 3 T brain MRI, the authors demonstrated that the basal ganglia, thalamus, and neocortical atrophy predict slowed cognitive processing in MS.   |
| Zivadinov et al. (2012) <sup>44</sup>  | 233 MS (169 RRMS and 4 SPMS) and 126 controls   | Utilizing SWI-filtered phase images, the authors assessed subcortical GM structure in patients with MS compared to control subjects, and reported abnormal phase in patients with MS in a number of GM regions, especially in the pulvinar nucleus of thalamus, indicative of higher iron content in patients with MS, which was related to more severe lesion burden and brain atrophy.   |

Abbreviations: ALS = amyotrophic lateral sclerosis; CIS = clinically isolated syndrome; DTI = diffusion tensor imaging; GM = gray matter; MRS = magnetic resonance spectroscopy; MS = multiple sclerosis; MTR = magnetization transfer ratio; NAA = N-acetylaspartate; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SDGM = subcortical deep gray matter; SPMS = secondary progressive multiple sclerosis; SWI = susceptibility-weighted imaging; WM = white matter.



**Figure 1** Coronal section through the posterior thalamus, secondary progressive multiple sclerosis

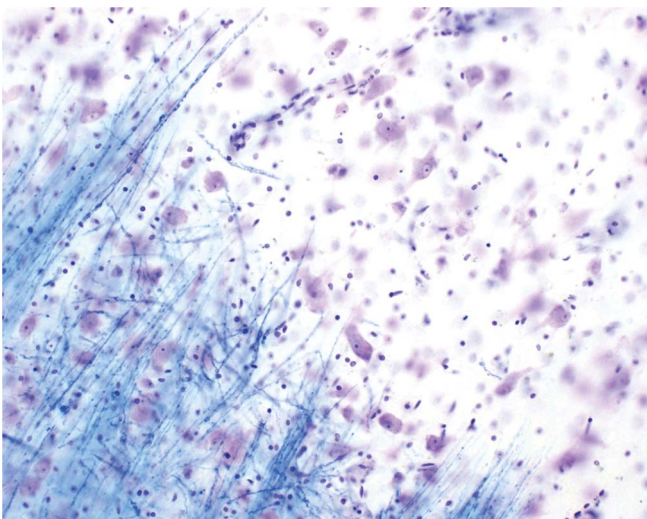


Focal chronic lesions are present in the right pulvinar nuclei and the lateral posterior nucleus of the thalamus (arrowheads), the latter with a remyelinating fringe. Demyelination is also present in the deep gray matter of the right caudate nucleus in association with an adjacent chronic white matter lesion. Additionally, there is a leukocortical lesion in the subiculum of the right hippocampal formation (arrow), diffuse demyelination of the left hippocampus proper (asterisk), and involvement of the periaqueductal gray matter. Classic small focal white matter lesions are present in the white matter, including the corpus callosum. Luxol fast blue.

likely substrate underlying this finding in both NAWM and NAGM, although diffusion of soluble cytokines from nearby focal lesions, or a primary innate immune response, are possible contributors.

**Pathology of focal lesions.** Histopathologic characterization of the thalamic lesions (figure 1) recapitulates the

**Figure 2** Border zone of a chronic thalamic lesion, secondary progressive multiple sclerosis



The gray matter lesion (top right) is devoid of myelin (stained blue) and hypocellular. Comparison with adjacent normal-appearing gray matter (bottom left) discloses a reduction in the number of neurons and a paucity of cells with oligodendrocyte morphology (Luxol fast blue).

spectrum of active, chronically demyelinated, and remyelinated pathologies observed in the WM. Chronic lesions, completely devoid of myelin (figure 2), predominate in the few existing pathologic descriptions, and exhibit a relatively subdued astrocyte reaction as indicated by glial fibrillary acid protein immunohistochemistry.<sup>8</sup> Within rare active lesions, the intensity of the macrophage infiltrate mirrors myelin density and therefore varies according to location within the thalamus. Similar to changes demonstrated in cortical GM lesions of autopsy cases,<sup>22–24</sup> both adaptive (T and B cell perivascular and parenchymal infiltration) and innate (microglial activation/macrophage infiltration) inflammation in the thalamus is constrained when compared with classic active WM lesions,<sup>8</sup> a factor that potentially limits neuroaxonal injury in evolving lesions. However, this view has been recently challenged by Lucchinetti et al.,<sup>3</sup> who demonstrate significant cortical GM inflammation in biopsy cases of early MS. Sampling bias in both early biopsy and end-stage autopsy studies may explain these discrepant findings; larger neuropathologic studies of the subcortical GM structures are required in order to corroborate or refute these observations.

**Neuronal pathology.** Thalamic pathology in MS cannot be viewed in isolation. As a discrete, symmetric brain structure with widespread cortical and subcortical connections, the thalamus provides the ideal neuropathologic (and MRI) substrate for examining neurodegeneration in MS. Cifelli et al.<sup>7</sup> examined the thalami of 10 patients with MS (9 progressive, 1 relapsing) and demonstrated a reduction in both thalamic volume (21%) and nonlesional neuronal density (22%) vs age- and gender-matched controls, confirming their *in vivo* MRI observations in a separate cohort of patients with secondary progressive MS. A similar degree of neuronal loss was subsequently described in nonlesional mediodorsal thalamic nucleus,<sup>8</sup> raising the possibility that neuronal loss is a retrograde event consequent to axonal transection in WM tracts projecting from the thalamus, or secondary to transsynaptic deafferentation of thalamic neurons. Altered neuronal morphology has also been described in the lateral geniculate nucleus (LGN) of the thalamus,<sup>25</sup> which receives projections from axons in the optic tract. The authors describe significant variation and an overall reduction in neuronal size in the parvocellular, but not magnocellular, layers of the LGN, which they attribute to retrograde damage resulting from differential susceptibility of small diameter axons (in the optic tract) to MS-related injury. It seems unlikely that Wallerian or transsynaptic degeneration is the sole cause of neuronal damage in the thalamus. Direct injury from diffusible cytokines, oxidative stress, excitotoxicity, and CD8 T-cell–mediated cytotoxicity are all contenders, particularly in cases with identifiable focal inflammatory lesions. Alteration in neuronal

morphology and size within demyelinated thalamic GM lesions compared with adjacent nonlesional GM supports this hypothesis.<sup>8</sup> Finally, surviving neurons within subcortical GM lesions invariably shed their satellite oligodendrocytes, potentially diminishing trophic support and disrupting the perineuronal microenvironment. In particular, perineuronal glutamate homeostasis may be dysregulated by the loss of glutamate transporter-expressing satellite oligodendrocytes.<sup>24</sup>

#### NEUROIMAGING CHARACTERISTICS OF THALAMIC INVOLVEMENT IN MS

Due to inherent structural differences between GM and WM and as a result of differences in inflammation characteristics, cortical GM lesions seem to maintain a normal water proton concentration and, unlike WM lesions, are not typically detectable as T2 hyperintense foci on MRI.<sup>26</sup> However, thalamic lesions are usually more visible than cortical lesions, likely because the thalamus is normally more densely myelinated. The introduction of double inversion recovery (DIR) in the study of MS may play an important step in refining the conspicuity of GM lesions.<sup>6</sup> By suppressing the signal from normal WM and CSF, DIR sequences provide excellent differentiation between GM and WM.<sup>27</sup> In a series of recently published studies from the Amsterdam (Netherlands)<sup>6</sup> and Padova (Italy)<sup>28</sup> groups, DIR imaging most frequently identified cortical lesions in male patients, progressive MS, and in those with CSF IgG oligoclonal bands. However, it is now evident that DIR imaging detects only a fraction of the real burden of cortical GM pathology that is present in patients with MS, with an average sensitivity of only 18%.<sup>29</sup> Therefore, although pathologically validated DIR scoring indicates a high specificity for the detection of GM lesions, the sensitivity is very low, with a false-positive rate of at least 10%.<sup>29,30</sup> The value of DIR in the detection of lesions in subcortical GM lesions was not investigated.

Contemporary investigations have focused on determining the extent of cortical and subcortical GM pathology in patients presenting with a first clinically isolated inflammatory demyelinating syndrome (CIS),<sup>11–13,31–33</sup> or following conversion to clinically definite MS.<sup>14,34</sup> It has been reported that global and cortical GM volume measures are not sensitive enough to detect GM atrophy at the time of the initial attack.<sup>31</sup> Therefore, GM atrophy studies in patients with CIS have increasingly turned to regional segmentation techniques to identify specific structures with a stronger predilection for disease susceptibility and conversion to clinically definite MS. A number of independent studies have shown that loss of volume in the thalamus is one of the earliest and most prominent signs of subcortical GM pathology when patients present with CIS.<sup>11–14,31,33,35</sup> Progressive atrophy of the thalamus (figure 3) has been shown in all different MS disease types<sup>12,13,15,36,37</sup> and

thalamic volume loss has also been detected in pediatric patients with MS.<sup>37–40</sup>

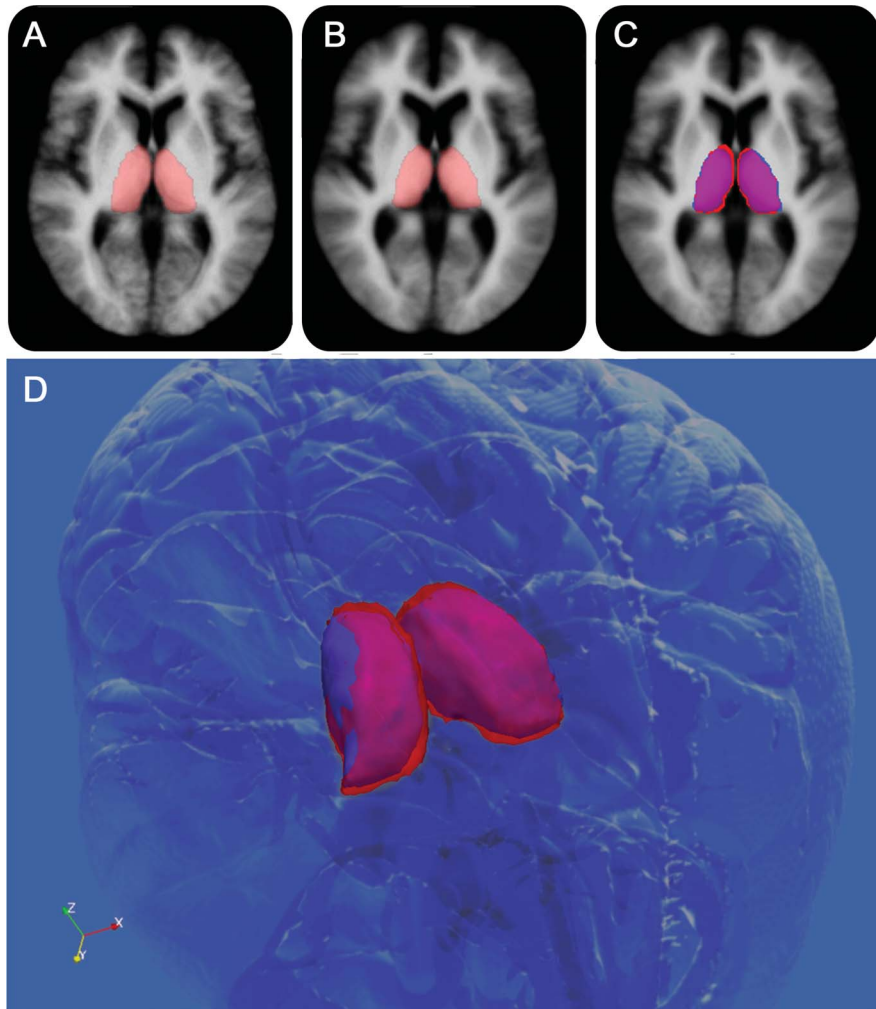
In a recent study of 42 patients with CIS, it was demonstrated that deposition of iron, as estimated by susceptibility-weighted imaging (SWI), in the thalamus and the pulvinar nucleus of the thalamus may precede the development of structure-specific thalamic atrophy at MS clinical onset.<sup>41</sup> This finding has to be confirmed in future studies; however, it is in keeping with mounting evidence derived from T2 hypointensity,<sup>42,43</sup> SWI,<sup>44</sup> and relaxometry<sup>45</sup> studies that showed that iron overload is dominant in the thalamus of patients with MS. One can hypothesize that a vicious cycle involving proinflammatory cells, atrophy of the thalamus, and possible iron accumulation may occur throughout the course of MS. Characterizing the temporal and dynamic interplay of these potential pathobiologic mechanisms from the first clinical onset mandates further investigation; however, at this time there is no definitive answer for the role of iron in relation to thalamic damage in patients with MS.

A number of diffusion-weighted or tensor,<sup>11,46</sup> magnetization transfer,<sup>46–49</sup> and magnetic resonance spectroscopy<sup>7,50,51</sup> imaging studies have investigated the extent of thalamic damage in patients with MS with various disease types (table). All suggested that there may be a common mechanism for WM axonal loss and thalamic neuronal injury related to thalamocortical pathways. One study of 24 patients with CIS sought to determine whether the association between WM lesions and thalamic atrophy at first clinical onset is related to connectivity of these fibers.<sup>11</sup> Diffusion tensor imaging (DTI) fiber tracking was used to create probabilistic templates of thalamocortical WM projections (figure 4A), and to define lesional thalamocortical WM tracks (figure 4B). There was a 10-fold higher density of lesions in thalamocortical projections compared to other brain WM regions. Using a stepwise linear regression model, DTI metrics within lesional thalamocortical tracks and thalamocortical lesion volume accounted for 66% of the variance in thalamic volume, while none of the MRI metrics outside thalamocortical regions contributed to thalamic volume. The authors suggested that focal MS lesions could cause distal WM injury and such damage could, at least in part, lead directly to thalamic neuronal and volume loss.

Taken together, these studies suggest that there is an urgent need for future longitudinal studies investigating the relationship between WM lesion accumulation, thalamic iron deposition, atrophy development, and microstructural alterations using nonconventional MRI metrics from the earliest clinical onset.

**CLINICAL MANIFESTATIONS** Clinically, thalamic involvement in MS manifests with a spectrum of diverse abnormalities, which range from fatigue and movement disorders to painful syndromes and cognitive decline.

**Figure 3** Comparison of thalamic segmentations



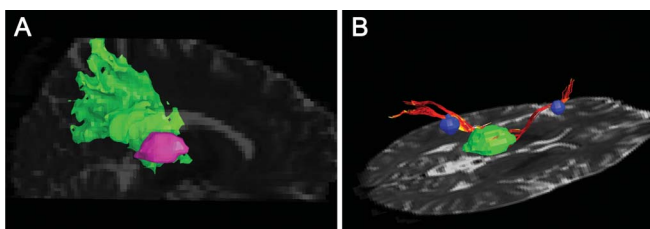
Comparison of thalamic segmentations between 26 healthy controls (HC) (age- and sex-matched) (A) and 98 patients with relapsing-remitting multiple sclerosis (MS) (B). (C) Voxel-wise differences between the groups, with magenta representing common areas, red HC-only areas, and blue MS-only areas. Individual patient images were coregistered into the Montreal Neurological Institute 152 space for visualization. A 3D view (D) shows that the MS thalami are smaller overall and slightly shifted away from the midline (most likely by global atrophic processes).

Fatigue is perhaps the most common and disabling symptom of patients with MS and is defined as an overwhelming feeling of a lack of both mental and physical

energy. Up to 80% of patients with MS are affected by fatigue, which interferes with a patient's quality of life.<sup>52</sup> Despite significant effort to elucidate the pathogenic mechanisms of fatigue in patients with MS, our knowledge remains marginal, with many unanswered questions. Neuroimaging studies have significantly contributed to the analysis of the pathogenesis of fatigue in MS<sup>36,53</sup> and have revealed functional abnormalities of neuroanatomic pathways involving frontal cortex, basal ganglia, and thalamus.<sup>36,54</sup>

A number of movement disorders have been described in association with MS,<sup>55</sup> which include tremor, parkinsonism, myoclonus, chorea, and paroxysmal dystonia. Paroxysmal dystonia is a painful manifestation of MS that usually presents with unilateral dystonic posture, precipitated by voluntary movement, tactile stimuli, or hyperventilation. Zenzola et al.<sup>56</sup> reported 2 patients with MS with paroxysmal dystonia and thalamic lesions. Both

**Figure 4** Representative 3D rendering example of fiber tracking from diffusion tensor imaging and voxel-based morphometry in multiple sclerosis



(A) Example of a probabilistic thalamoparietal template. The Montreal Neurological Institute transformed map is coregistered into the patient space; the thalamoparietal region of interest (ROI) is in green and the thalamus ROI in pink. (B) The figure shows 2 thalamocortical fiber tracks (red) seeded through white matter lesions (blue) connecting the thalamus (green) and the cortex (not shown).



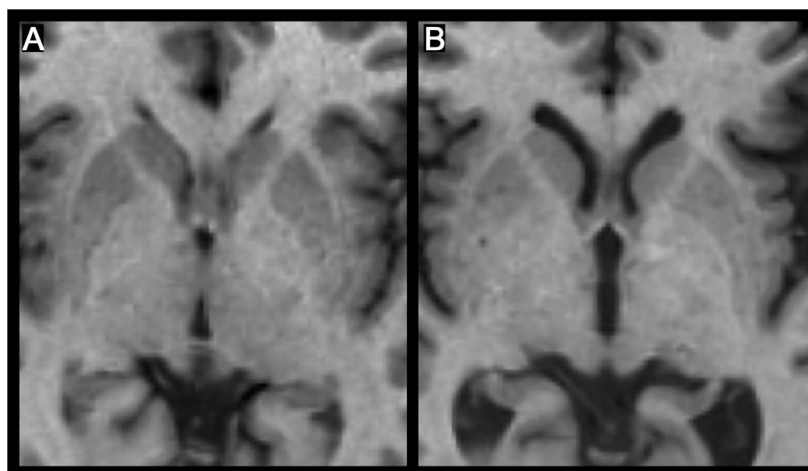
of these patients had developed demyelinating thalamic lesions contralateral to the paroxysmal symptoms.

Cognitive impairment is perhaps the most devastating and difficult to treat clinical manifestation of thalamic involvement in MS. In 2004, Benedict et al.<sup>57</sup> investigated associations between conventional brain MRI metrics and cognitive function in patients with MS. Contrary to expectation, third ventricle width was most strongly associated with several validated neuropsychological tests. Noting the recent evidence of thalamic atrophy in MS,<sup>7</sup> it was speculated that this finding was driven by atrophy (i.e., ex vacuo dilatation of the third ventricle) of the surrounding thalamic structures (figure 5). The hypothesis was directly investigated by tracing thalami from coronal 3D images, the boundaries being determined with an edge-finding tool and manual adjustment.<sup>16</sup> The raw thalamic volumes were then normalized as a ratio to intracranial volume. Analysis revealed a 16.8% reduction in volume in patients with MS compared to controls. In addition, thalamic fraction was the most significant MRI predictor of consensus standard<sup>58</sup> tests of memory and processing speed. These results were recently replicated in a larger, independent sample using the FIRST technique.<sup>59</sup> A similar theme has recently emerged in the pediatric MS literature. While Mesaros et al.<sup>60</sup> found similar whole brain parenchyma and GM volumes between patients and controls, voxel-based morphometry analysis and statistical parametric mapping detected clusters of reduced GM concentration in the thalamus. Correlations with disease duration and the Expanded Disability Status Scale (EDSS) were not, however, significant. The authors acknowledged that EDSS does not adequately assess cognitive ability. When

neuropsychological testing was applied to a pediatric sample,<sup>40</sup> patients with MS again were found to have significantly lower thalamic volume. This time, however, volume loss was the most significant MRI predictor of cognition compared to other MRI metrics. As in the earlier adult literature,<sup>16,57</sup> the degree of correlation was robust, with  $r$  values ranging from 0.6 to 0.7. A notable observation from both lines of research is that cognitive dysfunction in multiple spheres has been consistently associated with thalamic atrophy in children and adults with MS. In the pediatric study,<sup>40</sup> the correlation between thalamus volume and IQ was  $r = 0.68$ . The thalamic fraction or thalamic normalized volume represents a novel approach to quantifying regional GM volume, although it has to be acknowledged that the measure is crude from a neuropsychological perspective. The various nuclei in the thalamus have very different afferent and efferent connections to various brain regions and, as such, mediate disparate functions. Examining correlations with the anterior nucleus, which has rich connections with multiple frontal cortex areas, may shed more light on the link between thalamic pathology and neuropsychological involvement in MS.

**DISCUSSION** Cortical and subcortical GM involvement is a critically important contributor to the disease process in MS and leads to significant cognitive disability and other potentially devastating neurologic problems in these patients. Thalamic pathology, similar to the cortical pathology, appears to be present in MS from very early on, including at the CIS stage and in pediatric MS. In the progressive phase of MS, which is poorly explained by focal inflammatory WM demyelination, cortical and subcortical GM pathology including

**Figure 5** Thalamic atrophy and third ventricle width in multiple sclerosis



Thalamic atrophy is closely related to third ventricle width, as seen in these images of a patient with relapsing-remitting multiple sclerosis (MS) (A) and a patient with secondary progressive MS (B). Both patients have a disease duration of 14 years, and both images are of the same slice in stereotactic Montreal Neurological Institute 152 space.

neuronal and axonal degeneration are the likely substrates for accumulating cognitive and motor dysfunction that characterizes long-standing disease. Further research is needed to elucidate the pathologic processes that lead to MRI-detectable thalamic involvement in the early stages in MS and to characterize its role in disease progression. Existing information about thalamic involvement in MS stems mainly from neuropathologic and neuroimaging studies that have a limited number of subjects and contain no clear practical implications for clinicians. Therefore, larger longitudinal studies are required to assess the validity, accuracy, and sensitivity of these preliminary observations. We also recommend that serial measurement of thalamic volume be utilized as a biomarker in MS clinical trials to assess the patient's response to investigational therapeutic agents.

Finally, future neuropathologic MS studies in conjunction with advanced neuroimaging of GM involvement in general, and the thalamus in particular, should include new imaging techniques such as DIR, volumetric inversion recovery T1-based or phase-sensitive sequences, molecular or metabolite imaging, and high-field and ultrahigh-field MRI to further characterize relevant pathogenic mechanisms associated with disease progression over the short and long term.

#### AUTHOR CONTRIBUTIONS

Alireza Minagar, Michael H. Barnett, Ralph H.B. Benedict, Daniel Pelletier, Istvan Pirko, Mohamad Ali Sahraian, Elliot Frohman, and Robert Zivadinov substantially contributed to the concept and design of the study. Alireza Minagar, Michael H. Barnett, Ralph H.B. Benedict, and Robert Zivadinov drafted the article, while Daniel Pelletier, Istvan Pirko, Mohamad Ali Sahraian, and Elliott Frohman revised it critically for important intellectual content. All authors had access to the data.

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#### DISCLOSURES

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