

# The value of including thalamic atrophy as a clinical trial endpoint in multiple sclerosis

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Multiple sclerosis (MS) features a substantial white matter (WM) pathology in the brain, which manifests as focal lesions and reduced volume (or atrophy) compared with healthy controls. In addition, extensive gray matter (GM) atrophy is strongly prevalent in MS and highly clinically relevant but can be difficult to measure, especially in a clinical setting.<sup>1</sup> Recent work has shown clear patterns of GM atrophy in patients with MS<sup>2</sup> that are focused on brain network hubs, i.e., regions that are strongly connected with the rest of the brain. These areas are important for cognitive decline and disability progression and include the thalamus<sup>3</sup> and other regions belonging to the default-mode<sup>2,4</sup> and motor networks.<sup>2</sup> There has been a recent surge of interest in the thalamus, with some hope that thalamic atrophy and its associated dysfunction may be a treatment target of especially high potential<sup>3</sup> because thalamic atrophy can be measured relatively easily. The value of including thalamic atrophy as a trial endpoint in clinical trials with disease-modifying treatment in MS is emerging.<sup>5</sup>

In this issue of *Neurology*®, Gaetano et al.<sup>6</sup> present their post hoc analysis of 2 randomized placebo-controlled phase III trials (FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis [FREEDOMS] and FREEDOMS II) of fingolimod, a second-line treatment option for MS in most countries. Fingolimod consists of a sphingosine-1-phosphate receptor modulator that sequesters lymphocytes in lymph nodes, preventing their entry into the brain. Fingolimod reduces the annual rate of brain volume loss in patients with relapsing-remitting MS by approximately one-third relative to that in individuals receiving placebo or intramuscular interferon beta-1a.<sup>7</sup> This new analysis of the FREEDOMS and FREEDOMS II trials describes the effect of fingolimod in reducing regional volume loss, thereby extending and completing previous reports.

Gaetano et al. confirmed that fingolimod reduces the overall brain volume loss by about one-third (31.7%) at a clinical dosage of 0.5 mg. In addition, it has an effect on reducing the deep GM volume loss by 14.5% and the thalamic volume loss by 26.1% over 2 years. No significant effect on cortical atrophy was detected. Baseline T2 lesion volumes predicted thalamic volume loss. A lower thalamic volume at baseline was associated with disability progression, regardless of treatment.

The results from this study are an important contribution to the development of MRI endpoints for clinical trials because they demonstrate that the added value of including regional measures such as thalamic volume as outcome measures in clinical trials is substantial. The addition of such regional volumes is especially beneficial if they show a faster rate of change than whole-brain volume loss and their measurement error is relatively small. This study suggests that reanalyses of existing datasets with newer analysis techniques are attractive and should be pursued.

The mechanism by which fingolimod reduces the volume loss in the deep GM and the thalamus in MS remains unclear. Lesions within the thalamus are not that common and do not correlate well with thalamic atrophy,<sup>8</sup> suggesting that effects in other compartments such as the WM may be the causative factor for thalamic damage. The present article presents additional support for

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this hypothesis; the strong correlation between thalamic volume loss and baseline T2 lesions suggests that structural disconnection is the cause of thalamic atrophy. Given that the thalamus is one of the most important hubs in our brain, the chance that WM lesions will affect tracts connected to the thalamus is considerable, inducing a progressive disconnection syndrome over time. This concept of a network-based neurodegeneration may explain the early presentation of thalamic atrophy,<sup>3</sup> whereas the apparent later involvement of cortical areas and the subsequent acceleration of GM atrophy in progressive MS<sup>9</sup> may be the result of a further exhaustion of the brain network, leading to an eventual network collapse.<sup>10</sup>

This study is one of the first to show a GM compartment-specific treatment effect but should nonetheless be treated with caution. The primary drawback of the study lies in the use of cross-sectional techniques to determine longitudinal atrophy rates, which is an important problem likely to be alleviated with newer longitudinal analysis tools currently being developed. In addition, there is the lack of regional cortical GM measurements and an absolute increase in WM volume in fingolimod-treated patients only, which may be due to a bias in the imaging analysis algorithm or to biological factors.

Some key unanswered questions remain. Is an early network disconnection indeed the primary cause of thalamic neurodegeneration in MS? Will this thalamic damage lead to a subsequent cortical network collapse (with atrophy on MRI) and acceleration of GM atrophy over time? The possibility of slowing down neurodegeneration in MS is therefore of high interest and novel. Longitudinal imaging studies are needed to better understand the underlying mechanisms leading to thalamo-cortical neurodegeneration in MS and to identify whether thalamic atrophy is a suitable trial endpoint to be added to whole-brain atrophy measures.

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