Commentary for *Brain* on Steenwijk et al. "Cortical atrophy patterns in multiple sclerosis are non-random and clinically relevant"

What lies beneath grey matter atrophy in multiple sclerosis?

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Over the last 20 years, there have been remarkable advances in our understanding of pathogenic mechanisms in multiple sclerosis (MS), particularly those responsible for relapses and remissions. Over the same period a series of increasingly more effective treatments have become available that suppress relapses. However there has been a conspicuous lack of success treating progressive MS, which eventually affects most people with the condition, and is associated with the greatest disability. This has led to a reappraisal of pathological processes underlying progressive MS, and the recognition that pathology is more extensive and complicated than formerly thought.

Previously, a commonly held view of MS was of a multi-focal and multi-phasic immune-mediated white matter inflammatory demyelinating disorder, and indeed the suppression of such a process has underpinned the major progress in disease modifying treatment to date. However, it is now abundantly clear that in progressive MS, demyelinating lesions may be as extensive in grey matter as they are in white matter, and that there is substantial and widespread neuro-axonal loss, not only in white matter lesions but also in normal-appearing white matter, and in both the cortical and deep grey matter. It is also clear that grey matter pathology is present in early relapsing-remitting MS and increases with time. Neuro-axonal loss is now thought to be responsible for a major proportion of irreversible progressive disability in MS, but its causes are poorly understood, particularly when it occurs in the grey matter.

Brain atrophy in MS, as measured during life by MRI, is likely to reflect neuro-axonal loss (although other factors that can affect brain tissue volumes, especially when assessing short term changes, should be borne in mind). Loss of brain tissue does not occur uniformly, and in progressive MS it is most apparent in brain grey matter, affecting some cortical and deep grey matter regions more than others [Bendfelt et al., 2011]. *In vivo* MRI-clinical correlation studies have identified significant associations of grey matter atrophy with cognitive impairment, physical disability and progressive MS that are independent of associations with other imaging abnormalities, such as white matter lesion load. All-in-all, there are compelling reasons to try to better understand the mechanisms of grey matter atrophy and the neurodegeneration that it reflects.

In this issue of *Brain*, Steenwijk and colleagues report on their work looking at patterns of cortical grey matter atrophy in MS. They used source-based morphometry (SBM), an evolution of the widely used voxel based morphometry (VBM) approach. Both SBM and VBM identify regional disease effects on MRI scans without first specifying where to look (Figure 1). However, whereas VBM looks for regions that are consistently different between groups, SBM looks for regions where MRI features tend to vary together, and then determines how these are weighted in different groups. In practical terms, this means that SBM may be more sensitive to distributed but connected regional disease effects, as occurs when a brain network is damaged. SBM has the potential to provide useful insight into the pathogenesis and pathophysiology of MS, but its interpretation is challenging, as exemplified by the present study.

Consistent with previous VBM studies, the SBM analysis confirms that grey matter atrophy does not occur evenly throughout the cortex. However, it also shows that underlying this are overlapping regional 'patterns' of non-random cortical atrophy. The authors hypothesise that these atrophy patterns are initiated by the tract-mediated effects of white matter lesions on cortical 'hubs' (cortical regions centrally located in structural networks), with subsequent network-mediated (trans-synaptic) degeneration then extending from these hubs. Previous studies support such a network-based interpretation [Calabrese et al., 2015], but do not necessarily exclude alternative explanations (Table 1). The tract-mediated effects of white matter lesions may themselves directly result in non-random cortical changes: lesions preferentially accrue in certain white matter regions [Brownell and Hughes, 1962], axonal transection will be more likely in tracts traversing these regions, and so cortical neurodegeneration (and atrophy) due to secondary anterograde or retrograde degeneration will be greater in regions connected with these tracts.

Other mechanisms that may contribute to non-random grey matter neurodegeneration (and by implication cortical atrophy) need not be mediated at all via network or white matter tract degeneration. Meningeal inflammation, targeted grey matter immune processes, and regional metabolic vulnerability could all plausibly cause non-random regional neuronal loss and atrophy (Table 1). It is also possible that multiple mechanisms are at work, resulting in multiple patterns of non-random cortical atrophy.

The Steenwijk study also demonstrates that the relationship between cortical pathology and neurological impairments is not straightforward. Of the ten cortical thickness patterns found, four were independently linked with variations in EDSS scores, but only one of these was significantly associated with MS. This raises the possibility that natural variation in cortical networks may also significantly influence clinical outcomes in people with MS. This concept is not without precedence, for example there is already evidence that people with a higher maximal lifetime brain growth are relatively protected against the cognitive deficits in MS [Sumowski et al., 2014].

Having shown that there are multiple spatial patterns underlying cortical grey matter atrophy in MS, we now need to determine what lies beneath them. Pursuing a structural network-mediated hypothesis, in the present study whole brain white matter measures explained at most 20% of the variation in cortical thickness patterns ([Steenwijk *et al.,* 2015], Table 3). However, as the authors point out, this may under-

estimate the true association as tract-specific links may be diluted in the global white matter measures employed by the study. A pattern-by-pattern analysis of cortical regions and the white matter tracts that connect them would be informative. Being a single time-point study, Steenwijk and colleagues were also not able to investigate the temporal relationship of abnormalities within a network or between regional grey matter and their associated white matter tracts. Longitudinal studies with similar types of regional analysis could elucidate the sequence of events, and provide evidence for abnormalities that are causal and others that are consequential. Indeed, a recent study in primary progressive MS reports white matter tract abnormalities preceding changes in tissue integrity in anatomically linked grey matter (assessed with magnetisation transfer ratio measures; [Bodini et al., 2015]), which would be consistent with at least some of the grey matter pathology in this form of MS being secondary to white matter tract degeneration.

In summary, Steenwijk and colleagues have identified an important new feature of MS cortical grey matter atrophy: that it not only occurs in some cortical regions more than others but also that regions of predilection can be linked in a non-random way. There could be several explanations for these findings, and elucidation of these would be worthwhile given the clinical importance of grey matter atrophy in MS, and the potential to find new mechanisms for rationally based therapies that aim to prevent this striking neurodegenerative aspect of the disease.

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Table 1: Potential mechanisms of non-random regional cortical neuro-degeneration (and by implication cortical atrophy) in multiple sclerosis

Mechanism	Description
Network mediated	It has been shown that structural changes occur in the occipital cortex after optic neuritis, consistent with trans-synaptic neurodegeneration [Audoin et al. 2006]. Trans-synaptic degeneration in brain networks could lead to non-random patterns of cortical atrophy.
Axonal transection in white matter tracts	Axonal transection is common in acute inflammatory demyelinating white matter lesions [Calabrese et al. ,2015]. White matter lesions tend to accrue in watershed regions (for example around the lateral ventricles) [Brownell & Hughes, 1962] and so their tract-mediated effects on cortical grey matter (secondary neurodegeneration and atrophy) will be not be random.
Meningeal lymphoid-like aggregates	Lymphoid-like meningeal aggregates occur particularly in progressive MS [Magliozzi et al., 2006], are associated with cortical neurodegeneration and subpial cortical demyelination [Magliozzi et al., 2006 and 2010], and are located mainly in the cingulate gyrus, temporobasal and frontobasal cortices [Kutzelnigg et al. ,2006]; it is plausible that they could cause non-random regional cortical atrophy.
Targeted immune processes	CD8+ T cells are seen in MS cortical lesions, and have been linked with neuronal damage. MHC I expression differs between neuronal sub-populations [Calabrese et al., 2015], and so may result in non-random neurodegeneration and atrophy. Antigenic differences between neuronal sub-populations may also result in non-random regional effects.
Metabolic vulnerability	In more classical neurodegenerative conditions, such as Alzheimer's disease, regional differences in the tolerance of neuronal sub-populations to metabolic stress has been proposed as a cause of non-random cortical neuronal loss and atrophy [Saxena and Caroni, 2011]; such an effect might also operate with metabolic stress that occurs in MS [Witte et al., 2014].

Figure 1: Comparison of source and voxel based morphometry
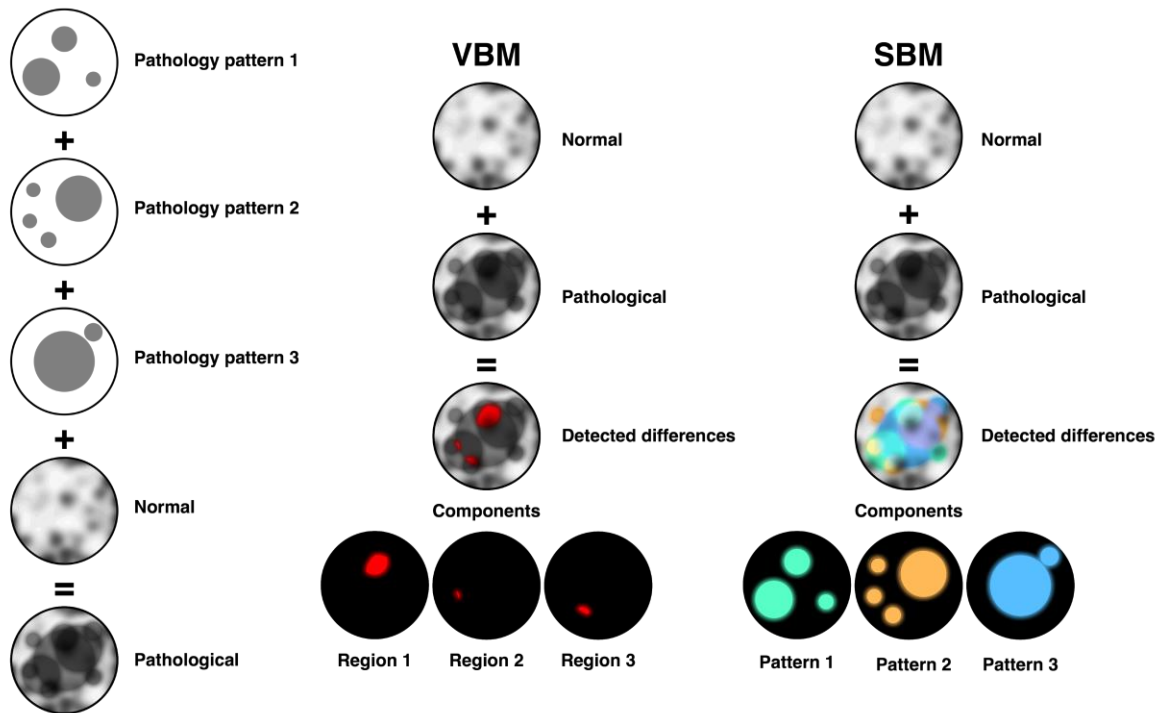
Left: Overlying pathological patterns combine with normal anatomy to produce the observed magnetic resonance images (MRI). Middle: Voxel based morphometry (VBM) assesses where there are regionally consistent differences in MRIs between groups that exceed a predefined threshold (regions in red on the VBM map). Right: Source based morphometry (SBM) first identifies regional patterns where tissue features are related (coloured regions on the SBM map), and then determines how these differ between groups.

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Disclosures