Reply: MRI findings of visual system alterations in Parkinson's disease

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Sir,

We were pleased that Arrigo and colleagues (Arrigo *et al.* 2017b) were impressed by our recent review (Weil *et al.* 2016) and that they found it an accurate description of clinical and functional features found in Parkinson's disease. Their recent work (Arrigo *et al.* 2017a) is a valuable contribution to the field. Their multi-modal approach that incorporates quantitative measures of white matter tracts provides important orthogonal information about the degenerative processes taking place early on in Parkinson's disease. Of interest, they found changes in the microstructure of white matter tracts that occur early on in the visual processing pathway, including in the optic radiation. Other groups have also made important contributions in this area (Pereira *et al.* 2014;Shine *et al.* 2015).

We agree that to better understand the pathological processes underlying Parkinson's disease it will be important to use techniques that go beyond grey matter volume measurements that are sensitive to neuronal death (Rossor *et al.* 1997). Effects of pathological accumulations within axons may be a more critical early feature of Parkinson's disease (Chung *et al.* 2009;Orimo *et al.* 2008) and these can be detected using quantitative measures of white matter microstructure. Where white matter and grey matter are measured concurrently in Parkinson's disease, changes in white matter microstructure precede grey matter loss (Duncan *et al.* 2016;Hattori *et al.* 2012). Focal mean diffusivity correlates with domain-specific loss of cognitive function in Parkinson's disease and occurs prior to reduction in fractional anisotropy or grey matter volume (Melzer *et al.* 2013).

Similarly, new technologies are emerging that are sensitive to alterations in brain tissue composition. These have the potential to provide important insights into the biological mechanisms of Parkinson's disease. For example, quantitative susceptibility mapping, which is sensitive to iron content, can detect abnormalities in brainstem and cortex in Parkinson's disease, that cannot be detected using conventional grey and white matter imaging (Acosta-Cabronero *et al.* 2017). Furthermore advances in diffusion imaging, such as neurite orientation dispersion and density (Zhang *et al.* 2012) and multi-shell global tractography (Christiaens *et al.* 2015) now allow detailed characterisation of white matter microstructure and white matter brain networks, respectively.

In parallel with these advances in image analysis is the mounting evidence that topological features of healthy brain networks can predict both grey and white matter loss in a range of neurodegenerative diseases (Seeley *et al.* 2009;Zhou *et al.* 2012;Mandelli *et al.* 2016). This represents a step change from the detection of group differences between patients and healthy populations to systems level mechanisms that can account for the selective vulnerability of specific brain regions in neurodegenerative disease. In this respect, connectomics and graph theoretical analysis approaches are providing important new insights into organisational principles that can account for selective vulnerability in Parkinson's disease. For example, Zeighami and colleagues (Zeighami *et al.* 2015) showed that intrinsic functional networks of the healthy brain and network proximity to the substantia nigra, the proposed disease epicentre in Parkinson's, could account for grey matter atrophy patterns in Parkinson's disease relative to controls. This provides evidence to support the model of cell-to-cell propagation of alpha synuclein in Parkinson's disease. These techniques are also proving to be particularly sensitive to early variations, with changes in connectivity patterns seen before differences can be detected using conventional measures (Pereira *et al.* 2015). Critically, some of the earliest network changes, seen even in drug naïve Parkinson's patients, are found in temporo-occipital regions and correlate with performance in visuo-perceptual measures (Luo *et al.* 2015).

These multi-modal approaches will be important in gaining a better understanding of the pathological processes that underlie Parkinson's disease and in determining the earliest neuroimaging signature of disease, in order to identify patients that may in future benefit from disease modifying treatments.

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