

Neuropathologically informed imaging of cortical grey matter lesions in MS – a pilot study

S Quigley¹, M.C. Yiannakas², P. Bede^{1, 3}, J. Meaney⁴, H. Kearney^{1, 5}

Affiliations:

1 Department of Neurology, St James's Hospital, Dublin, Ireland

2 NMR Research Unit, Queen Square MS Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom.

3 Computational Neuroimaging Group (CNG), TBSI, Trinity College Dublin, Ireland

4 Centre for Advanced Medical Imaging, St James's Hospital and Trinity College Dublin, Dublin, Ireland

5 Academic Unit of Neurology, Trinity College Dublin, Ireland

Correspondence:

Dr H Kearney, Academic Unit of Neurology, Trinity College Dublin

KEARNEYH@tcd.ie

Key words:

Multiple sclerosis, Cortical lesions, MRI, neuropathology

Abstract

Multiple sclerosis (MS) is frequently misdiagnosed based on MRI abnormalities detected in the brain white matter. Cortical lesions have been well described neuropathologically, but remain challenging to detect in clinical practice. Therefore, the ability to detect cortical lesions offers real potential to reduce misdiagnosis. Cortical lesions have been shown to have a predilection for regions with CSF stasis - such as the insula and cingulate gyrus. This pathological observation forms the basis of our current pilot MR imaging study, which successfully uses high spatial resolution imaging of these two anatomical regions to clearly identify cortical lesions in MS.

Introduction

Neuropathology of the multiple sclerosis (MS) brain shows extensive involvement of the grey matter, and lesions in the cortex may be seen *in vivo* using research magnetic resonance imaging (MRI) protocols, but technical limitations have hindered the translation to routine clinical practice (Bunyan 2014; Geurts and Barkhof 2008). This is a pertinent issue as the McDonald diagnostic criteria are heavily weighted towards the identification of white matter abnormalities (Thompson et al. 2018), and arising from this, misdiagnosis of other neurological diseases as MS remains a significant problem (Solomon et al. 2016).

To date, MRI studies that have focused on identifying grey matter lesions in MS have involved detailed whole brain assessments, but even so, only a subset of all neuropathologically identifiable lesions are typically seen (Geurts and Barkhof 2008).

To date imaging studies of cortical lesions in MS have focused on whole brain coverage, however, the evaluation of the spatial distribution of MS grey matter lesions post-mortem reveals a clear predilection of lesion burden to areas of the cortex surrounded by reduced cerebrospinal fluid (CSF) flow, such as the cingulate gyrus or insular cortex (Haider et al. 2016).

Based on this neuropathological observation, the objective of this study is the targeted evaluation of the insular cortex and cingulate gyrus *in vivo*. To assess this approach we used a PSIR sequence, as prior studies have shown the utility of this sequence for

cortical lesion detection in MS (Filippi et al. 2016; Sethi et al. 2012). However, two advantages of this sequence are: firstly, it can be acquired at high spatial resolution using a 3D-acquisition, and secondly the neuropathologically targeted approach with a reduced field of view did not compromise image quality.

The image resolution ($0.75 \times 0.75 \times 0.75\text{mm}^3$) in the current study was higher than a previous study incorporating the use of 2D-PSIR sequence with thicker slices (and associated partial volume effects), and was the study protocol was designed to facilitate a detailed review of the MS cortex (Sethi et al. 2012).

Methods

Participants

We recruited patients with MS and healthy controls (HC) from the MS Unit in St James's Hospital. Inclusion criteria: all people with MS fulfilled the 2017 McDonald criteria for diagnosis and had evidence of unmatched oligoclonal bands in CSF. Exclusion criteria: another brain disease or prior implantation of a ferromagnetic device or other contraindications for MRI. This study was approved by St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee; Ref No 840.

MRI acquisition

We invited all participants to attend for a brain scan using a 3T Achieva TX system (Philips Healthcare, Best, The Netherlands). Each participant had a 3D-phase sensitive inversion recovery (PSIR) scan, using the magnetisation prepared 3D T1 turbo field-echo (TFE) as the base sequence, and with a field of view (FOV) limited to

the anterior portion of the brain containing the two anatomical regions of interest. Scan parameters were as follows: voxel size = 0.75 x 0.75 x 0.75 (mm³), FOV = 110 x 110 (mm²), number of slices = 87, repetition time = 12ms, echo time = 5 ms, flip angle = 8° (PSIR flip angle = 5°), inversion delay time = 821ms, TFE factor = 128, number of excitations = 2, compressed sense factor = 2, total scanning time = 13:21min.

Image analysis

Cortical lesions were defined as hypo-intense to the surrounding normal cortex on PSIR images – this definition was derived from a prior report analysing cortical lesions with this sequence (Sethi et al. 2012).

Two experienced readers were provided with a list of anonymised exam numbers without any clinical details. The readers were instructed to review the PSIR image without reference to any prior imaging or laboratory reports. Based on this blinded assessment, each reader rated the scan as containing cortical lesions or not.

Statistical analysis

Based on the readers' assessment of the anonymised scans, we calculated the sensitivity and specificity for the detection of cortical lesions. This analysis did not incorporate the existing radiological diagnostic framework of identifying dissemination of space and time, as T2-weighted or gadolinium enhanced images were not included in the image analysis protocol.

Results

We recruited three people with relapsing remitting MS, two female, with a mean age of 51 ± 3 years and a median expanded disability status scale (EDSS) 3 (range 2-4). All three were on treatment with disease modifying drugs and none had a relapse or steroid exposure within a month of the scan. In addition, three healthy controls participated, two female, with a mean age of 33 ± 9.4 years. Demographic details are summarised in Table 1.

In the radiological review, both readers identified the presence of cortical lesions on all scans of people with MS, and no control scans were identified to have evidence of cortical lesions. An example of a cortical lesion and juxtacortical lesion are shown in Figure 1. In the identification of cortical lesions, the two readers had complete concordance in their results i.e., cortical lesions identified in all cases of MS and none in controls.

Discussion

This pilot study provides a novel application of an existing sequence (PSIR) to identify of cortical lesions in MS.

The approach in this current study differs from prior imaging studies of grey matter abnormalities in MS. The basis of this imaging study is the neuropathological distribution of cortical lesions and the MRI scans acquired focused on two anatomical regions known to have the highest distribution i.e. insular cortex and cingulate gyrus

(Haider et al. 2016). This differs from prior imaging MS grey matter imaging studies, where the whole brain is included in the imaging protocol (Hulst and Geurts 2011).

The results of the image analysis identified cortical lesions in each scan of a person with MS and none in controls, albeit in a small cohort. The targeted neuropathological basis to the imaging protocol improved identification of cortical lesions, validation of this approach will require future comparative study with whole brain acquisition to compare the yield of cortical lesion detection. Nonetheless, the current study does show the feasibility of the methodology with a reduced field of view, but doesn't address the important point of comparison with the diagnosis of T2-weighted high signal intensity abnormalities in the white matter on MRI or comparison with other brain diseases as only healthy controls were recruited owing to the developmental nature of the current pilot study.

Owing to the neuropathologically based hypothesis for the distribution of grey matter abnormalities, this led to a scan with a reduced field of view. However, we believe that this approach is positive, in terms of developing a 'framing effect' from a cognitive perspective (Tversky and Kahneman 1981). We believe that this more targeted review of two anatomical regions, rather than the whole brain, improved the decision making process in the determination of the presence or absence of cortical lesions.

Owing to the pilot nature of the current study a 2D sequence was not acquired to facilitate direct comparison, however, 3D acquisition has shown an increase in lesion detection with another inversion recovery sequence (FLAIR) over a 2D acquisition

(Bink et al. 2006). The increased contrast to noise ratio may also be a factor with PSIR using 3D acquisition to account for ready identification of cortical lesions.

There are some limitations to our current study. Firstly, the small sample size. Secondly, the study is based solely on the identification of cortical lesions and does not facilitate a comparison with the current diagnostic criteria using this modified imaging approach. Thirdly, the cohort recruited consisted of people with MS or healthy controls, and did not include people with other brain diseases. This current study addresses the feasibility of using a reduced field of view - guided by the neuropathology of MS - to identify cortical lesions. Whilst this was achieved using a PSIR sequence, a number of other sequences have been developed which can identify cortical lesions (Filippi et al. 2016), and adoption of a similar methodology may overcome the lack of widespread availability of PSIR on clinical scanners.

However, this present study was designed to be a pilot study, in order to establish the feasibility of the methodology from an imaging perspective. A future larger scale study is planned based on these data, and this will incorporate analysis of MS diagnostic criteria as well as inclusion of people with other brain diseases, such as migraine or other brain diseases that may display T2-weighted high-signal intensity abnormalities on MRI.

In conclusion, this pilot study uses a novel imaging approach guided by neuropathology to clearly identify cortical lesions in brain anatomical regions known to have the highest distribution in MS.

Author Contribution statement

MY wrote the exam card for sequence acquisition. SQ and PB analysed the MR images. JM provided clinical reporting of images. HK conceived the study design and supervised clinical data collection and image analysis.

Conflict of interest/Role of funding source

Declaration of competing interests

SQ, MY, PB, JM have no conflicts of interest. HK has received speaker and travel honoraria from Novartis, Teva, Biogen, and Roche.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We thank all the people enrolled in this study for giving their time to research.

References

- Bunyan, Reem. 2014. "Cortical Demyelination in MS." *Multiple Sclerosis and Related Disorders* 3(6): 768.
- Geurts, Jeroen JG, and Frederik Barkhof. 2008. "Grey Matter Pathology in Multiple Sclerosis." *The Lancet Neurology* 7(9): 841–51.
- Haider, Lukas et al. 2016. "The Topography of Demyelination and Neurodegeneration in the Multiple Sclerosis Brain." *Brain* 139(3): 807–15.
- Hulst, Hanneke E., and Jeroen J. G. Geurts. 2011. "Gray Matter Imaging in Multiple Sclerosis: What Have We Learned?" *BMC neurology* 11: 153.
- Sethi, Varun et al. 2012. "Improved Detection of Cortical MS Lesions with Phase-Sensitive Inversion Recovery MRI." *Journal of Neurology, Neurosurgery, and Psychiatry* 83(9): 877–82.
- Solomon, Andrew J. et al. 2016. "The Contemporary Spectrum of Multiple Sclerosis Misdiagnosis: A Multicenter Study." *Neurology* 87(13): 1393–99.
- Thompson, Alan J et al. 2018. "Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria." *The Lancet Neurology* 17(2): 162–73.
- Tversky, A., and D. Kahneman. 1981. "The Framing of Decisions and the Psychology of Choice." *Science (New York, N.Y.)* 211(4481): 453–58.

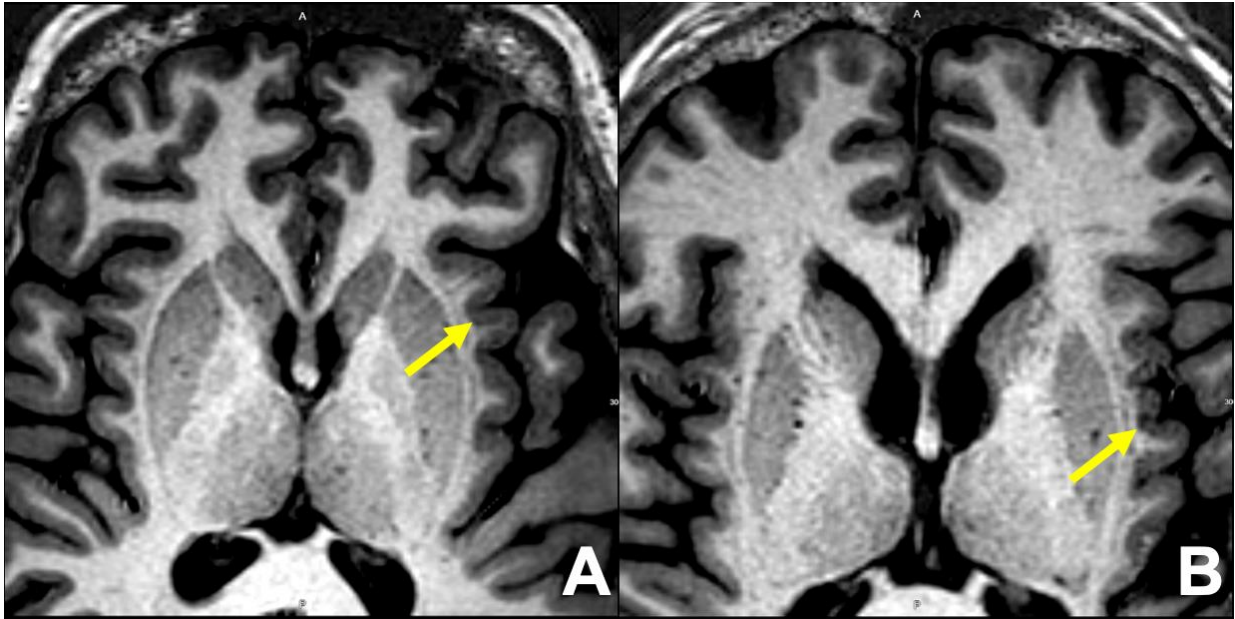


Figure 1: 3D-phase sensitive inversion recovery (PSIR) images showing example of (A) cortical lesion in the insula and (B) juxtacortical lesion. Lesions are highlighted by block arrows in both.

Table 1: Demographics of people with multiple sclerosis (MS) and controls recruited for this study

	MS	Controls
	N=3	N=3
Mean Age (\pm SD)	51 \pm 3	33 \pm 9.4
Sex (F:M)	2:1	2:1
Subgroup MS	RRMS	
Disease duration (years)	20 \pm 6.5	
Median EDSS (range)	3 (2-4)	
DMD	Interferon- β n=2, ocrelizumab n=1	
Scans with cortical lesions identified by two blinded raters	N=3	N=0

Abbreviations: RRMS - relapsing remitting multiple sclerosis; DMD - disease modifying drug; EDSS - expanded disability status scale.