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COMMENTARY

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Advanced MRI quantification of neuroinflammatory disorders

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1 | BACKGROUND

Neuroinflammatory disorders are characterized by the implications of both peripheral infiltration and local immune-mediated targeting of various central nervous system (CNS) components, which can typically contribute to neuroaxonal and glial degeneration, followed by gross atrophy (Gilhus & Deuschl, 2019). Whereas the diagnosis of neuroinflammatory disorders had previously been based on the clinical presentation of symptoms, we are now offered the opportunity to glimpse the processes in vivo using magnetic resonance imaging (MRI) (Gilhus & Deuschl, 2019). Moreover, conventional MRI allows for qualitative identification of neuroinflammation, and more recent advancements in this field now also enable quantitative monitoring of various neuroinflammatory and neurodegenerative processes (Kremer et al., 2015; Magnims et al., 2015). Multiple sclerosis (MS) is one of the most prominent chronic neuroinflammatory disorders and is characteristically defined by both focal and diffuse inflammatory-mediated demyelination and neuroaxonal degeneration (Reich et al., 2018). Despite a well-established understanding of typical conventional imaging MRI biomarkers for MS that thereby facilitate the diagnosis (Thompson et al., 2018), there remains a wide range of neuroinflammatory disorders and mimics with significant MRI-based imaging similarities that contribute to misdiagnosis (Geraldes et al., 2018). A multicenter study revealed that MS misdiagnosis resulted in the development of unnecessary disability in a significant proportion (31%) of patients due to the improper application of the McDonald diagnostic criteria (Solomon et al., 2016, 2019).

One of the foremost MS mimics to consider, which was previously considered to be a severe optic-spinal MS variant (Lennon et al., 2004, 2005), is the neuromyelitis optica spectrum disorders (NMOSD). This overlap is particularly due to the relapsing clinical nature of NMOSD, which shares considerable overlap with the relapsing–remitting (RRMS) subtype of MS and radiological features, as emphasized in Figure 1a (Geraldes et al., 2018; Solomon et al., 2021). Differentiating NMOSD from MS is of significant importance for patients, particularly considering that the treatment options and prognosis vary (Piehl, 2021; Wallach et al., 2021). Without proper diagnosis and subsequent treatment, approximately 50% of persons with NMOSD will require a wheelchair and have severe visual impairment within 5 years of their first symptoms, and approximately a third of will have died (Huda et al., 2019). The recent development of numerous promising disease modulatory therapies has provided a more positive outlook for those with NMOSD (Cree et al., 2019; Pittock et al., 2019; Traboulsee et al., 2020; Zhang et al., 2020). Importantly, NMOSD is distinct from the pathology of MS, in that the autoimmunity, for most, targets the astrocytic aquaporin 4 (AQP4) water channels along astrocytic end-feet that maintain the blood–brain barrier and brain-CSF interfaces rather than the myelin insulation axons, as in MS. The byproduct of AQP4-IgG antibody-mediated targeting is an astrocytopathy with increased water permeability, and cytokine release followed by the swelling of astrocytes (Chang & Chang, 2020). However, there is a portion of those with NMOSD who are seronegative for AQP4-IgG autoantibodies, and among them, a majority has been found to have

Abbreviations: ADEM, acute disseminated encephalomyelitis; AQP4, aquaporin 4; CNS, central nervous system; GM, gray matter; IgG, immunoglobulin; LETM, longitudinally extensive transverse myelitis; MOG, myelin oligodendrocyte glycoprotein; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; MS, multiple sclerosis; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorders; NODDI, neurite orientation density and dispersion imaging; q-MRI, quantitative magnetic resonance imaging; RRMS, relapsing–remitting multiple sclerosis; SLE, systemic lupus erythematosus.

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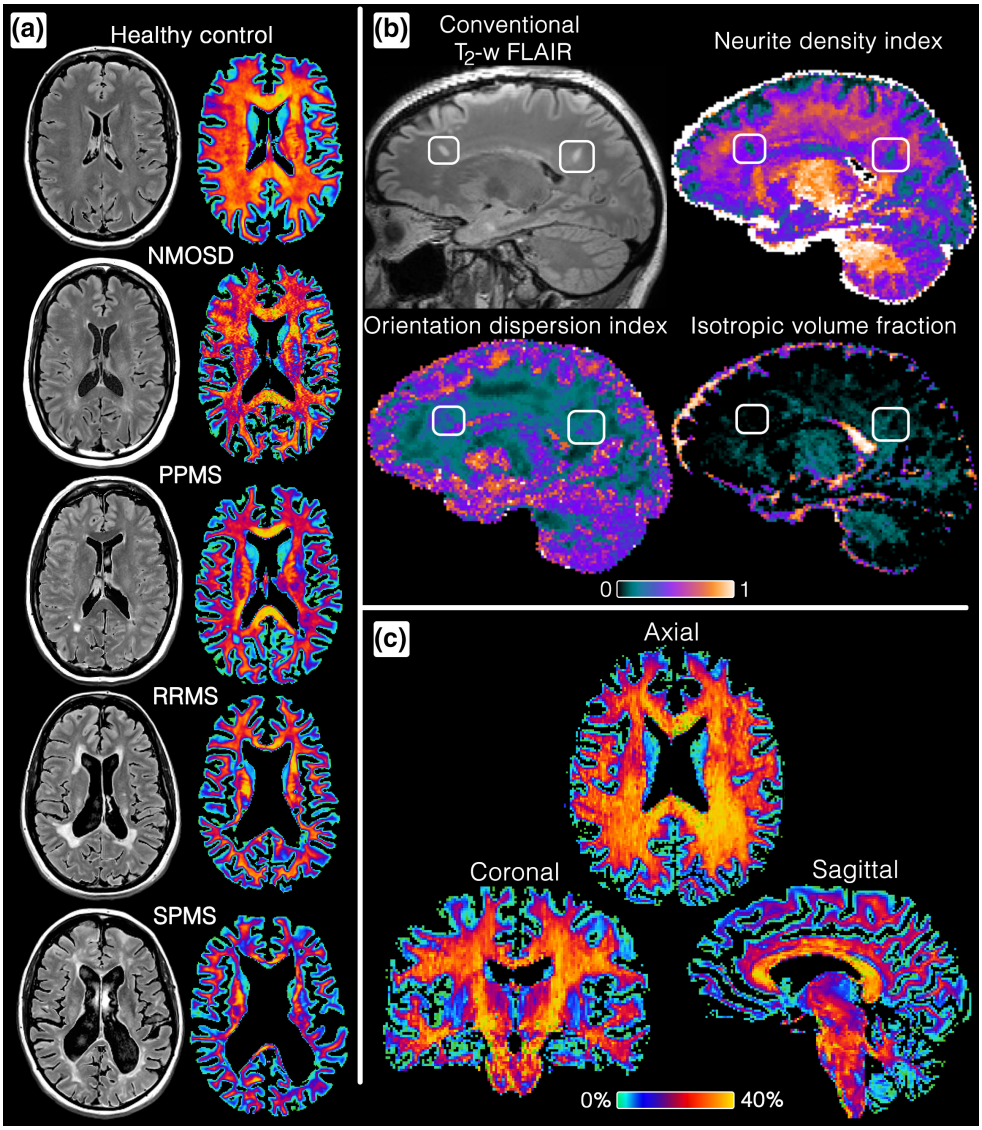

FIGURE 1 Advanced MRI quantification of myelin and neuroaxonal integrity in MS and NMOSD. (a) Myelin quantification: Synthetic 2D T_2-weighted FLAIR axial image and the corresponding 2D SyMRI-based myelin content map in: healthy control, 56-year-old female healthy participant; NMOSD ($AQP4^+$), a 60-year-old female participant; PPMS, a 53-year-old female participant; RRMS, a 40-year-old female participant, and SPMS, a 44-year-old female participant. (b) Neurite integrity: T_2-FLAIR image highlighting two apparently similar MS lesions in a young female with RRMS. NODDI reveals that the posterior lesion (right-most) is differentiated by less pronounced axonal loss, more edema, and heterogeneous microstructural integrity relative to the frontal lesion (left-most). The neurite density index is representative of neuroaxonal and glial densities. The isotropic fraction infers CSF or parenchymal edema. The orientation dispersion index is suggestive of axonal fanning or interneurite spacing. NODDI measures are a quantitative unitless scale of 0–1. (c) 3D Myelin quantification: Myelin maps from a newly developed 1.2 mm isotropic 3D SyMRI prototype (≈8 min acquisition) of a 30-year-old male, which represents an approximate 2.9× improvement in resolution relative to typical prior 2D SyMRI acquisitions at $1 \times 1 \times 5\,mm^3$ (accounting for slice gap in relative resolution). $AQP4^+$, aquaporin 4 seropositivity; FLAIR, fluid attenuated inversion recovery; mm, millimeter; NODDI, neurite orientation density and dispersion imaging; NMOSD, neuromyelitis optica spectrum disorders; PPMS, primary progressive multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

antibodies for myelin oligodendrocyte glycoprotein (MOG-IgG), developing MOG antibody disease (MOGAD). At last, acute disseminated encephalomyelitis (ADEM), another MS mimic disorder, is closely related to MOG-IgG and becoming well-recognized, particularly in children (Narayan et al., 2018).

The sensitivity of conventional MRI in identifying inflammation in the CNS has made MRI investigation a common clinical standard investigatory procedure following neuropathological suspicion (Albrecht et al., 2016). The importance of MRI as a paraclinical tool in the diagnosis of MS is exemplified in the most recent iteration of the McDonald criteria; where MRI can solely satisfy both diagnostic principles of dissemination of pathology in both time and space (Thompson et al., 2018). Diagnostically characteristic MS lesions will occur in periventricular, cortical/juxtacortical, and infratentorial

brain regions and the spinal cord (Bakshi et al., 2008; Thompson et al., 2018). Whereas characteristic MRI-based pathology in NMOSD will more often occur in the form of (i) periependymal brain lesions, (ii) extensive optic nerve lesions, and (iii) longitudinally extensive transverse myelitis (LETM) of the spinal cord (Solomon et al., 2021). However, conventional MRI lacks specificity to some of the various targets and processes associated with neuroinflammatory disorders. Moreover, conventional MRI, while sensitive and highly qualitatively valuable has limited quantitative comparison across imaging sessions. Therefore, the diagnostic and monitoring value of MRI across all neuroinflammatory disorders could be further improved by using advanced quantitative MRI (q-MRI) techniques that may provide additional insight into the disease and offer new diagnostic possibilities (Kremer et al., 2015; Magnims et al., 2015). Recent technological and hardware developments have allowed for more substantial probing of tissue integrity in the clinical setting (Granberg et al., 2016). Numerous non-conventional advanced q-MRI neuroimaging approaches have demonstrated utility in characterizing the primary pathological features of neurological disorders, specifically those with a significant neuroinflammatory and/or neurodegenerative component (Filippi et al., 2019). The value of q-MRI in predicting both physical and cognitive disability worsening in MS has been demonstrated to exceed that of conventional lesion volume measures (Ouellette, Mangeat, et al., 2020). Representative SyMRI myelin (rapid estimation of myelin, REMyDI) and neurite orientation density and dispersion imaging (NODDI) maps for healthy, MS, and NMOSD participants enrolled in our prospective studies are presented in Figure 1.

Historically, MS was stereotypically described as a neurological disease of the cerebral white matter. More recently, the majority of the field has begun to address gray matter (GM) pathology in MS. Notably through specific conventional cortical imaging sequences (at 3 T), phase-sensitive inversion recovery (PSIR), or double inversion recovery (DIR), to capture cortical lesions, but more sensitively at ultra-high field strength (7 T), typically by T_2^*-weighted imaging (Mainero et al., 2009). Gray matter pathology has been demonstrated to extensively occur in MS histologically (Lucchinetti et al., 2011), by 7 T MRI in the cortex (Treaba et al., 2019), and deep GM (Mehndiratta et al., 2021), while being related to clinical disability (Ouellette, Treaba, et al., 2020). Moreover, significant neuroaxonal degeneration (Granberg et al., 2017) and demyelination (Louapre et al., 2015) have been observed to occur beyond cortical lesions, as captured by q-MRI techniques. However, the patterns in which GM alterations occur in NMOSD relative to MS, particularly in early MS, remain undetermined.

There is a significant value in the application of non-conventional q-MRI techniques to characterize and map the contributing pathophysiological processes across neuroinflammatory disorders to better understand their dynamics, thereby supporting potential follow-up for serological testing in clinical cases where conventional MRI white matter signal abnormalities share neuroanatomical similarity. We can further our understanding of these relatively more recently identified neurological disorders by contrasting their patterns of pathology with disorders that are more frequently investigated, such as MS, as done here by Andica and colleagues.

2 | CONTRIBUTION OF THE PRESENT WORK TO THE FIELD

The findings of the present cohort by Andica and colleagues echo and expand upon findings from prior studies in MS and NMOSD. The neuroanatomical agreement across the nonconventional q-MRI techniques for tissue integrity underlines the significance and/or susceptibility of the limbic and paralimbic regions in both MS and NMOSD. In MS, reduced tissue integrity, by R2* or 1/T2*, has been observed in the limbic cortices to be related to physical and cognitive clinical disability (Wen et al., 2017). Interestingly, there have been numerous case reports of limbic encephalitis as an initial clinical presentation in AQP4-IgG$^+$ NMOSD (Seok et al., 2019) and MOG-IgG$^+$ ADEM (Uchigami et al., 2020). However, the reason for the neuroanatomical significance involvement of the limbic system in MS and NMOSD is less well-characterized. Here, Andica and colleagues present significantly lower neurite density in the cerebellar, limbic, and paralimbic cortices of participants with NMOSD relative to both healthy participants and those with RRMS. Take, for example, the parahippocampal cortex, a significant region in this study that was identified across DTI, NODDI, and myelin content metrics. The parahippocampus has extensive connectivity to various brain regions, including temporal, frontal, parietal cortices, and deep GM structures (Aminoff et al., 2013). Any severing of the intermedial connectivity could produce an indirect degeneration via Wallerian degeneration. Alternatively, in the parahippocampal region, there could be a differential expression of the primary pathological driver in NMOSD, AQP4, which has been shown to differ based on the ratio of astrocytic M1/M23 proteins (Eshaghi et al., 2016; Saji et al., 2013). Therefore, the difficulty lies in whether you are observing a reduction of tissue integrity (demyelination/axonal or astrocyte degeneration) due to primary disease-specific pathology or secondary degeneration following a distant lesion, which also has topological variance between MS and NMOSD. Longitudinal prospective studies that include a connectivity paradigm will be required to address this.

One of the more intriguing observations is the value of the NODDI neurite integrity metrics relative to the myelin quantification of SyMRI, not only across all comparisons but also particularly for the comparisons including participants diagnosed with RRMS, a demyelinating disorder. There have been prior studies on patients with early RRMS (>5 years disease duration) with diffusion-based imaging abnormalities, using the composite hindered and restricted model of diffusion (CHARMED) (De Santis et al., 2019; Mangeat et al., 2018; Toschi et al., 2019). Granted, the participants included here by Andica and colleagues are participants with RRMS rather than the more progressive subtypes, and therefore, there would, overall, be less demyelination. However, with a disease duration average exceeding 10-years and some more advanced EDSS scores,

I would have expected there to be some more group differences observed, particularly concerning healthy control participants. I believe this is most likely due to a combination of the region of interest and the sequence parameters. First, the region of interest, mainly the cortical gray matter, which can be appropriately described as the "cortical ribbon" a highly convoluted and thin structure that varies with a global cortical thickness to be approximately ≈2.5 mm in healthy individuals (Lemaitre et al., 2012) and roughly ≈2.3 in participants with MS (Ouellette, Treaba, et al., 2020). Therefore, to reasonably estimate the cortex, particularly by quantitative voxel-wise analysis, at the very least, one voxel should be able to mostly fit within the cortex, approximately 1.5 mm isotropic would be most ideal. Additionally, a true 3D sequence would be the most ideal approach as 3D imaging conventional imaging is the clinical standard for most sequences at most facilities.

3 | FUTURE CONSIDERATIONS

Certainly, moving forward, there needs to be diversification and expansion of enrollment to more fully account for the spectrum of disorders indicated in the grouping of NMOSD, namely, AQP4-IgG$^+$ NMOSD, MOG-IgG$^+$ (MOGAD), double seronegative NMOSD (AQP4-IgG$^-$ and MOG-IgG$^-$), and also comparable neuroinflammatory disorders, ADEM and systemic lupus erythematosus (SLE). There is sincere value for including other neuroinflammatory MS mimics, allowing the comparative differences across these neuroinflammatory disorders to shed light not only on their individual pathophysiology but identifying differences and shared observations across the disorders. There has also been increasing application of machine learning approaches with q-MRI data to support differential diagnosis between neuroinflammatory disorders that share imaging similarities (Mangeat et al., 2020). Comparative evaluation could potentially shed more light on these diseases' pathophysiological dynamics and facilitate the development of disease-specific biomarkers, as has been done for some of the relatively more recently identified MRI hallmark biomarkers being identified in MS, including chronic paramagnetic rim lesions (Absinta et al., 2016), cortical lesions (Mainero et al., 2009), and central vein lesions (Sati et al., 2016). Potentially moving forward, at higher field strengths (7 T) and more q-MRI techniques with larger cohorts, we can surmise the clinical value of stacking these unique biomarkers relative to other neuroinflammatory disorders.

There is a unique role of nonconventional and advanced q-MRI to support the imaging arm of large multisite cross-collaboration clinical research initiatives. The added research and clinical value are most emphasized in q-MRI techniques that have demonstrated: (i) histological validation, (ii) repeatability/reproducibility, and (iii) clinical utility. The development of 3D SyMRI imaging (Figure 1c) of the brain and spinal cord would hold value for future studies, specifically, for characterizing cortical pathology, as done here. The increased signal-/contrast-to-noise provided by ultra-high field 7 T MRI of the brain and spinal cord across neuroinflammatory disorders could provide heightened sensitivity in identifying pathological differences across disorders (Ouellette, Treaba, et al., 2020). Notably, 7 T MRI could be valuable in identifying the relationship between vasculature (T_2^* effect) and pathology as derived by paramagnetic disturbances related to iron distribution in susceptibility-weighted imaging (SWI) in neuroinflammation. The rarity of some of these neuroinflammatory disorders shifts the emphasis away from "quantity" toward that of "quality" and richness of the data, thereby providing a heightened necessity to layer in additional advanced multimodal techniques in these cohorts. To that end, positron emission tomography (PET) imaging of inflammation (^{11}C-PBR28) mediated by activated microglia/macrophages has been found to be increased in the GM (Herranz et al., 2016, 2019) and cerebellum (Barletta et al., 2019) of those with MS, which shares considerable overlap with the observations described in this study by Andica and colleagues.

Recent technological advancements now allow for faster imaging and the ability to stack more q-MRI techniques into a clinical acquisition without the drawback of increasing the scanning duration. A few of the recent more promising techniques include simultaneous multislice (Ye et al., 2016), wave-controlled aliasing in parallel imaging (Wave-CAIPI) (Bilgic et al., 2015), compressed sense (Ning et al., 2016), and time-resolved imaging for ultra-fast multiparametric quantitative MRI (3D-EPTI) (Wang et al., 2022). Large-scale real-world q-MRI data sets would support clinical decision-making, not only in the diagnosis but also in treatment monitoring. This is well-evidenced in MS, where increasingly effective immunomodulatory treatments that virtually completely block new focal lesion formation; the next boundary is to develop novel therapies to reduce residual innate inflammation and/or facilitate remyelination (Piehl, 2021). This observation is comparably echoed by the recent successive introduction of disease modulatory therapies in AQP4-IgG$^+$ NMOSD (Cree et al., 2019; Pittock et al., 2019; Traboulsee et al., 2020; Zhang et al., 2020). The subsequent analysis of where/how these therapies modulate specific disease processes using in vivo q-MRI can allow for a more individualized approach for patients with neuroinflammatory diseases, as well as providing a crucial evaluation tool for novel drug development. This is well demonstrated for those with seronegative (AQP4$^-$) NMOSD, where there still needs to be further therapeutic development. However, developing therapeutic target-specific ex vivo q-MRI validation pipelines is a key aspect to bridge q-MRI and gold-standard ex vivo histopathological observations. Cataloging of an extensive well-curated library of in vivo, post-mortem in situ, and ex vivo multimodal q-MRI alongside expansive gold-standard histological inquiry would provide the volume of data necessary to disentangle some of the significant pathogenic contributors of these neuroinflammatory disorders.

There is a significant need to investigate the applicability of advanced brain and spinal cord q-MRI in neuroinflammatory disorders to better understand the radiological presentation and pathophysiological dynamics and to develop tools that could potentially help facilitate the development and benchmarking of neuroprotective therapies. Therefore, I implore those who have substantial rich unique data sets to seek out others with complementary strengths and who share common goals to help those in need with these neurological

disorders. The answers to many of these debilitating pathologies lie across the bridges of expansive multicenter collaborational efforts.

Russell Ouellette has written the article and derived the corresponding visual element and has received honoraria for lecturing from Novartis.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Russell Ouellette has written the article and derived the corresponding visual element and has received honoraria for lecturing from Novartis.

PEER REVIEW

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