NeuroImage 167 (2018) 438–452

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Mapping of thalamic magnetic susceptibility in multiple sclerosis indicates decreasing iron with disease duration: A proposed mechanistic relationship between inflammation and oligodendrocyte vitality

Ferdinand Schweser [a,b,*], Ana Luiza Raffaini Duarte Martins [a], Jesper Hagemeier [a], Fuchun Lin [a], Jannis Hanspach [a,c], Bianca Weinstock-Guttman [d], Simon Hametner [e], Niels Bergsland [a], Michael G. Dwyer [a], Robert Zivadinov [a,b]

[a] Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY, USA
[b] Center for Biomedical Imaging, Clinical and Translational Science Institute, University at Buffalo, The State University of New York, Buffalo, NY, USA
[c] Institute of Radiology, University Hospital Erlangen, Erlangen, Germany
[d] Jacobs Multiple Sclerosis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY, USA
[e] Department of Neuroimmunology, Center for Brain Research, Medical University of Vienna, Vienna, Austria

ARTICLE INFO

Keywords:
Quantitative susceptibility mapping
QSM
Iron
Multiple sclerosis
Thalamus

ABSTRACT

Recent advances in susceptibility MRI have dramatically improved the visualization of deep gray matter brain regions and the quantification of their magnetic properties *in vivo*, providing a novel tool to study the poorly understood iron homeostasis in the human brain. In this study, we used an advanced combination of the recent quantitative susceptibility mapping technique with dedicated analysis methods to study intra-thalamic tissue alterations in patients with clinically isolated syndrome (CIS) and multiple sclerosis (MS). Thalamic pathology is one of the earliest hallmarks of MS and has been shown to correlate with cognitive dysfunction and fatigue, but the mechanisms underlying the thalamic pathology are poorly understood.

We enrolled a total of 120 patients, 40 with CIS, 40 with Relapsing Remitting MS (RRMS), and 40 with Secondary Progressive MS (SPMS). For each of the three patient groups, we recruited 40 controls, group matched for age- and sex (120 total). We acquired quantitative susceptibility maps using a single-echo gradient echo MRI pulse sequence at 3 T. Group differences were studied by voxel-based analysis as well as with a custom thalamus atlas. We used threshold-free cluster enhancement (TFCE) and multiple regression analyses, respectively. We found significantly reduced magnetic susceptibility compared to controls in focal thalamic subregions of patients with RRMS (whole thalamus excluding the pulvinar nucleus) and SPMS (primarily pulvinar nucleus), but not in patients with CIS. Susceptibility reduction was significantly associated with disease duration in the pulvinar, the left lateral nuclear region, and the global thalamus. Susceptibility reduction indicates a decrease in tissue iron concentration suggesting an involvement of chronic microglia activation in the depletion of iron from oligodendrocytes in this central and integrative brain region. Not necessarily specific to MS, inflammation-mediated iron release may lead to a vicious circle that reduces the protection of axons and neuronal repair.

1. Introduction

Atrophy of the thalamus is one of the earliest hallmarks of brain pathology in Multiple Sclerosis (MS) (Audoin et al., 2009; Bergsland et al., 2012; Calabrese et al., 2011; Henry et al., 2008, 2009; Ramasamy et al., 2009; Zivadinov et al., 2013), which correlates with physical disability (Rocca et al., 2010) and fatigue (Calabrese et al., 2011), and continues with the progression of the disease (Bergsland et al., 2012; Henry et al., 2008; Preziosa et al., 2017; Ramasamy et al., 2009). Thalamic atrophy has also been shown to correlate with cognitive dysfunction (Batista et al., 2012; Bergsland et al., 2016; Bisecco et al., 2017; Houtchens et al., 2007) in MS, which is in line with other studies showing an association

* Corresponding author. Buffalo Neuroimaging Analysis Center, Department of Neurology, University at Buffalo, 875 Ellicott St., Buffalo, NY 14203, USA.
E-mail address: schweser@buffalo.edu (F. Schweser).

https://doi.org/10.1016/j.neuroimage.2017.10.063
Received 28 July 2017; Received in revised form 24 October 2017; Accepted 27 October 2017
Available online 31 October 2017

Abbreviations

Avg	Average
CI	Confidence Interval
CIS	Clinically Isolated Syndrome
DAB	Diaminobenzidine
Dd	Disease Duration
DGM	Deep Gray Matter
EDSS	Expanded Disability Status Scale
FOV	Field of view
FWE	Family-Wise Error
GRE	Gradient Recalled Echo
GT	Global Thalamus
IBA-1	Ionised Calcium-Binding Adapter Molecule 1
IQR	Interquartile Range
IR-FSPGR	Fast Spoiled Gradient-Echo Pulse Sequence With Inversion Recovery
LNR	Lateral Nuclear Region
MNR	Medial Nuclear Region
MS	Multiple Sclerosis
NAWM	Normal Appearing White Matter
NC	Normal Controls
PET	Positron Emission Tomography
Ppb	Parts Per Billion
PUL	Pulvinar
QSM	Quantitative Susceptibility Mapping
R_2*	Effective Transverse Relaxation Rate
RRMS	Relapsing-Remitting MS
SPMS	Secondary Progressive MS
SWI	Susceptibility-Weighted Imaging
T_1w	T_1-Weighted
TFCE	Threshold-Free Cluster Enhancement
WM	White Matter

between thalamocortical connectivity and diverse functions of higher level cognitive processes (Fama and Sullivan, 2014), including attention, speed of information processing, working memory, and episodic memory processes (Hughes et al., 2012; Philp et al., 2014; Ystad et al., 2010, 2011).

However, despite its potential direct involvement in cognitive dysfunction, disability, and disease progression, comparatively little is known about the mechanisms of thalamic involvement in MS. One reason for the relative scarcity of mechanistic studies is that the thalamus exhibits similar MR-relevant properties as circumjacent white matter (WM) tissues (Kanowski et al., 2014; Tourdias et al., 2014), like T_1 and T_2 relaxation times and proton density, which hampers *in vivo* investigations with clinical MRI. In particular, the anatomical complexity of the human thalamus, which consists of approximately 100 distinct cell groups or nuclei (Axer and Niemann, 1994) with distinct connectivity profiles (Fama and Sullivan, 2014; Postuma and Dagher, 2006; Sherman and Guillery, 2013a,b), has been inaccessible *in vivo* until recently. The increasing availability of higher magnetic field strengths and advanced MRI acquisition and analysis techniques has enabled imaging studies with improved resolution and sensitivity toward new biophysical tissue properties, recently enabling a more detailed *in vivo* assessment of the thalamus (Abosch et al., 2010; Behrens et al., 2003; Bisecco et al., 2015; Unrath et al., 2008; Wiegell et al., 2003). These developments have increased the interest in exploring the involvement of the thalamus in neurological diseases (Minagar et al., 2013).

Quantitative Susceptibility Mapping (QSM) is such a novel advanced MR-based technique (Duyn, 2013; Haacke et al., 2015; Liu et al., 2015; Reichenbach et al., 2015; Schweser et al., 2011, 2016; Wang and Liu, 2015) that allows for the precise anatomical depiction of intra-thalamic nuclei and even allows quantifying tissue property alterations with high spatial resolution (Deistung et al., 2013) and reproducibility (Deh et al., 2015; Feng et al., 2017; Lin et al., 2015; Santin et al., 2017) at clinically feasible scan times. Various histological validation studies have demonstrated that *magnetic susceptibility,* the quantity provided by QSM, reflects the tissue concentrations of paramagnetic iron complexes (Langkammer et al., 2012; Schenck, 1992; Stüber et al., 2014, 2016; Zheng et al., 2013) as well as, in an opposite way, myelin (Groeschel et al., 2016; Schweser et al., 2011; Stüber et al., 2014) and calcium (Chen et al., 2014b; Schweser et al., 2010; Straub et al., 2017; Stüber et al., 2014). Within the MS research, QSM is increasingly being used for the characterization of iron load in the deep gray matter (DGM) (Al-Radaideh et al., 2013; Blazejewska et al., 2015; Hagemeier et al., 2017; Langkammer et al., 2013; Ropele et al., 2017; Rudko et al., 2014; Schmalbrock et al., 2016) and lesions (Bian et al., 2016; Chen et al., 2014a; Cronin et al., 2016; Eskreis-Winkler et al., 2014; Harrison et al., 2016; Kakeda et al., 2015; Li et al., 2016; Wisnieff et al., 2015; Zhang et al., 2016).

In the present study, our central hypothesis was that MS is associated with increased magnetic susceptibility in the thalamus. We further hypothesized that the most substantial differences between patients and controls would be observed in the pulvinar (PUL) nucleus and the lateral nuclear region (LNR) because of potential *trans*-synaptic degeneration emerging from the motor and visual cortices, regions that are highly affected by MS (Calabrese et al., 2007) and maintain relatively rich structural connectivity with the PUL and LNR. We based our hypothesis on a significant body of literature on DGM iron accumulation in MS (Ropele et al., 2017; Stephenson et al., 2014; Stüber et al., 2016) as well as the well-documented fact that MS leads to demyelination and atrophy. Both the accumulation of iron and loss of myelin increase the tissue's magnetic susceptibility, which leads to a hyper-intense appearance on the susceptibility maps. Furthermore, thalamic atrophy, which occurs early in the course of MS due to demyelination and neurodegeneration, would increase the observed susceptibility simply because of a condensation of the iron present in the tissue.

Several previous MRI studies indicated increased *thalamic* iron in MS (Drayer et al., 1987; Rudko et al., 2014; Zivadinov et al., 2012), such as our previous work with susceptibility-weighted imaging (SWI) MRI, in which PUL was atrophied and signal changes indicated an increased susceptibility early in the disease course of pediatric and clinically isolated syndrome (CIS) patients (Hagemeier et al., 2012, 2013b). Further support for our hypothesis was provided by previous studies using positron emission tomography (PET) (Banati et al., 2000; Herranz et al., 2016; Kauzner et al., 2016; Rissanen et al., 2014) and histopathology (Haider et al., 2014; Vercellino et al., 2009) indicating increased microglia activation and influx of highly iron-laden macrophages in the thalami of MS patients, respectively. Also, histopathologic evidence exists for substantial focal demyelination and neuronal loss in the thalamus (Cifelli et al., 2002; Haider et al., 2014; Vercellino et al., 2009). Overall, previous literature strongly argued for a susceptibility increase in the thalamus of MS patients.

To test our hypothesis, we used QSM to examine intra-thalamic alterations of magnetic susceptibility in patients with CIS and MS as compared to matched healthy controls. QSM combines two crucial properties for the study of such a complex structure as the thalamus: first, it delivers high resolution images and enables the depiction of anatomical details that have been inaccessible with other *in vivo* imaging techniques, forming the basis of a volumetry of the thalamic substructures. Second, QSM represents a unique tool to assess the tissue composition via quantitative measurements of the tissue's magnetic susceptibility. We combined volumetry and susceptibility quantification to dissect thalamic iron and myelin mass changes from apparent susceptibility increases that