Published in final edited form as:

Alzheimers Dement. 2018 August ; 14(8): 998–1004. doi:10.1016/j.jalz.2018.03.007.

Evidence of demyelination in mild cognitive impairment and dementia using a direct and specific MRI measure of myelin content

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Abstract

INTRODUCTION—We investigated brain demyelination in aging, mild cognitive impairment (MCI), and dementia using magnetic resonance imaging (MRI) of myelin.

METHODS—Brains of young and old controls, and old subjects with MCI, Alzheimer's Disease (AD), or vascular dementia (VD) were scanned using our recently developed MWF mapping technique, which provides greatly improved accuracy over previous comparable methods. Maps of myelin water fraction (MWF), a direct and specific myelin measure, and relaxation times and magnetization transfer ratio (MTR), indirect and nonspecific measures, were constructed.

RESULTS—MCI subjects showed decreased MWF compared to old controls. Demyelination was greater in AD or VD. As expected, decreased MWF was accompanied by decreased MTR and increased relaxation times. The young subjects showed greater myelin content compared to the old subjects.

DISCUSSION—We believe this to be the first demonstration of myelin loss in MCI, AD, and VD using a method that provides a quantitative MRI-based measure of myelin. Our findings add to the emerging evidence that myelination may represent an important biomarker for the pathology of

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All authors report no disclosures.

MCI and dementia. This study supports the investigation of the role of myelination in MCI and dementia through use of this quantitative MRI approach in clinical studies of disease progression, relationship of functional status to myelination status, and therapeutics. Further, mapping MWF may permit myelin to serve as a therapeutic target in clinical trials.

Keywords

Mild Cognitive Impairment; Alzheimer's Disease; Vascular dementia; Demyelinating disease; MRI

1. INTRODUCTION

Mild cognitive impairment (MCI) may represent a prodromal phase of Alzheimer's Disease (AD), which is characterized by a progressive decline in cognitive abilities, including memory, language, and judgment [1]. The development of non-invasive markers for MCI and pre-symptomatic stages of AD would provide critical prognostic information and, perhaps most importantly, a therapeutic target. Moreover, such markers may provide important mechanistic information regarding the etiology of cognitive decline and dementia.

Amyloid-beta ($A\beta$) accumulation has been recognized as a hallmark of AD pathology for over two decades. The formation of $A\beta$ plaques and tau tangles are associated with degeneration of neurons and neuronal synapses [2–4]. The amyloid hypothesis states that these effects form the underlying pathophysiologic basis for AD, and has been supported both by theoretical considerations and various experimental results. For example, removal of $A\beta$ plaques was found to relieve cognitive deficits in animal models [5, 6]. However, the validity of the amyloid hypothesis for human AD has been questioned. There is a weak correlation between amyloid burden and cognition, and more than 30% of cognitively normal older individuals have significant amounts of $A\beta$ and tau deposition [7, 8]. Further, anti- $A\beta$ interventions have failed to stop or attenuate the progression of the disease [9–16].

Partly due to the limitations of the amyloid hypothesis, it has been proposed more recently that alterations in myelination are an important pathophysiologic correlate of AD and MCI [17–20]. Myelin is an electrical insulator essential for action potential conduction and for transporting trophic support to the neuronal axons of the central nervous system (CNS) [21]. Patterns of myelination represent an important biomarker for CNS diseases and neurodevelopment [22, 23]. Thus, loss of oligodendrocytes, the cells forming and maintaining the myelin, and subsequent demyelination may serve as a trigger leading to pathological events that may impede regional CNS connectivity. In fact, studies have demonstrated that common genetic and environmental risk factors directly contribute to the cognitive deficits and demyelination seen in MCI and AD, as well as in normal aging [17–20]. This myelin model, introduced by Bartzokis and colleagues [17–20], suggests that the breakdown of myelin may promote the deposition of $A\beta$ fibrils, which in turn causes further myelin breakdown and, ultimately, neurodegeneration. Indeed, a central role for myelination disorders in MCI and dementia, as a complement to the amyloid hypothesis, has been put forward to account for the failure of clinical trials targeting amyloid [9–11, 24], and shifts

the focus of AD pathology from the burden of discrete lesions to an emphasis on brain circuitry [25, 26], given the role of myelin in signal transmission in the CNS.

The critical importance of connectivity within the brain has been greatly highlighted by the NIH Human Connectome Project [27]. This complex project seeks to integrate MR anatomic imaging, resting- and task-related functional MR imaging, genetic, and behavioral data to further elucidate the underpinnings of the effect of brain connectivity patterns on functional outcomes. Thus, the emphasis is on the integration of all aspects of brain architecture and function. Of note, myelin mapping is one of the key components of the MRI sequences used; although indirect measures were performed (see below), this nevertheless highlights the central importance of myelination patterns in current concepts relating brain structure to cognitive function. We believe that the reliability of further investigations of myelin patterns will be substantially augmented by use of more advanced metrics for myelination, such as the new approach to MWF we have developed, and in this paper have applied to cognitively impaired and unimpaired adults. Understanding the patterns of demyelination in MCI, AD, and normal aging may be of substantial clinical relevance, and may provide important insights into the progression from cognitively normal to MCI and from MCI to AD. Finally, myelin may serve as a preclinical biomarker for the early detection of MCI and AD.

Alterations in myelin content in aging, MCI, AD, and vascular dementia (VD) have been investigated using magnetic resonance imaging (MRI). However, these studies have relied upon indirect and nonspecific measurements of brain myelin content, including diffusion tensor imaging, magnetization transfer ratio (MTR), longitudinal relaxation time (T_1) and transverse relaxation time (T_2) [17–20, 28–33]. These modalities indicate patterns of myelination, but do not depict myelin content quantitatively or specifically. For example, T_2 is sensitive to tissue properties such as hydration, macromolecular content, temperature, flow, and architectural structure, so that it cannot serve as a specific marker of myelin. Similar comments apply to diffusion, MTR, and T_1 . In addition, if local myelin content decreases by a given amount, this is not reflected quantitatively by a proportionate change in any of these outcome measures. This complicates interpretation of such imaging results. In contrast, multicomponent analysis such as the multicomponent driven equilibrium single-pulse observation of T_1 and T_2 (mcDESPOT) technique [34–41] allows for direct measures of myelin through quantification of myelin water fraction (MWF). In fact, MR-derived MWF correlates with myelin content better than do other, indirect myelination markers [42, 43]. In addition, using mcDESPOT MRI, Dean and colleagues [34] have recently shown an association between MWF and cerebrospinal fluid biomarkers of AD for asymptomatic individuals with genetic risk factors for AD. Their findings suggest that amyloid pathologies significantly influence white matter microstructure, and represent an important step toward elucidating the relationship between myelin degradation and A β pathology. Further, direct correlation of MRI-based MWF mapping and histologic evaluation of myelin has been established [42]. Overall, MRI mapping of MWF has emerged as an important approach to myelination studies.

Our recent improvements in mcDESPOT using Bayesian Monte Carlo (BMC) approaches have led to a new, powerful, means of generating high quality MWF maps [38–40]. Here, we report the first evidence of myelin loss in MCI through direct MR imaging of myelin

content. We also show that our direct measure is sensitive to demyelination in normal aging, AD, and VD.

Overall, our results indicate that the quantitative MRI approach to myelin mapping in the human brain presented here may be applied to clinical investigations of the relationship of myelination to progression, functional status, and response to therapy of patients with MCI and dementia. This supports the use of these MWF measurements as a potential biomarker and therapeutic target in clinical trials of interventions for cognitive decline and dementia.

2. METHODS

2.1. Subjects

Eleven participants were studied: three young non-impaired (1 male; mean $\pm$ SD age = 40 $\pm$ 5.6 years), three old non-impaired (3 males; age = 88 $\pm$ 5.5 years), three old with MCI (2 males; age = 89 $\pm$ 5 years), one old with AD (female, 72 years old), and one old with documented VD (male, 75 years old). Experimental procedures were performed in compliance with our local Institutional Review Board and subjects or their surrogates provided written informed consent.

2.2. Data acquisition and analysis

Scans were performed on a 3T Philips MRI system (Achieva, Best, The Netherlands) as described previously [34, 35, 38–40]. SPGR/bSSFP were acquired with flip angles (FAs) of [2 4 6 8 10 12 14 16 18 20] / [2 7 11 16 24 32 40 60]°, echo times (TEs) of 1.37/2.8 ms, and repetition times (TRs) of 5/5.8 ms, and matrix size = 150×130×94. To correct for B₁ inhomogeneity [44], two fast spin-echo (FSE) images were acquired with FAs of 45° and 90°, TE = 102 ms, TR = 3000 ms and matrix size = 90×81×35. Paired SE images with (S_w) and without (S_{wo}) a radiofrequency off-resonance prepulse (1100 Hz; B₁ = 13.5 μ T), were acquired for MTR mapping. Images were obtained with TR = 100 ms, TE = 2.1 ms, FA = 18° and matrix size = 120 $\times$ 104 $\times$ 75. All images were acquired with field-of-view of 240 mm $\times$ 208 mm $\times$ 150 mm.

For each subject, scalp, ventricles, and other non-parenchymal regions within the images were eliminated using the FSL software [45], with parameter maps generated for the remaining regions of interest. T_1 and T_2 maps were calculated from the SPGR and bSSFP imaging datasets as in previous studies [34, 35, 38, 40]. MTR maps were generated from the paired SE images outlined above through $MTR = 1 - S_w/S_{wo}$. Finally, MWF maps were generated from the SPGR and bSSFP imaging datasets using the BMC-mcDESPOT analysis [38–40].

3. RESULTS

Our analysis showed a substantial decrease in MWF in several brain regions of the participants diagnosed with MCI as compared to the old non-impaired participants (Figs. 1–2). Furthermore, we found a substantial decrease in MWF in several brain regions of the individuals diagnosed with AD or VD (Fig. 1). For most subjects, these regions included the medial temporal lobes, parietal lobes, the splenium and genu of the corpus callosum, and the

white matter regions surrounding the frontal and posterior aspects of lateral ventricles. As expected, decreased MWF was accompanied by decreased MTR and increased T_1 and T_2 , although as noted above these conventional measures are nonspecific to myelin content (Figs. 1–2).

Furthermore, our results indicate overall greater MWF in the brains of the young compared with the old participants (Fig. 2). This was accompanied by increased MTR and decreased T_1 and T_2 . These findings were visible in multiple brain regions within the frontal, parietal, occipital, and temporal lobes of both hemispheres. We note that visual inspection of parameter maps shows substantial variation in derived values of MWF, T_1 and T_2 in different brain regions between individuals within the same group (Fig. 2).

4. DISCUSSION

We implemented our recently-developed BMC-mcDESPOT approach to measure MWF in non-impaired young and old participants, and in individuals with MCI, AD, or VD. MWF showed direct evidence of demyelination in several brain regions of MCI subjects, with corresponding decrease in MTR and increase in T_1 and T_2 (Fig. 1). The decrease in MTR is attributable to decreased water proton exchange between a more restricted macromolecular environment and less-restricted intra- and extra-cellular water [17–20, 28, 29, 46]. Increases in T_1 and T_2 are attributable to a decrease in the lipid-rich myelin sheath and a corresponding increase in water mobility. The results of these indirect measurements of MWF, namely MTR, T_1 and T_2 , were in good agreement with the literature [29, 30, 32–34, 46].

The degree and extent of myelin loss was different between the MCI subjects, with Subject #2 showing much greater demyelination as compared to the other subjects (Fig. 1). This underscores the heterogeneity of MCI and the necessity to extend our subject cohort for quantitative regional-based analysis. Further, longitudinal studies may indicate whether the extent of demyelination in MCI indeed represents a prognostic indicator for conversion to dementia, given the greater extent of myelin loss observed in subjects with AD or VD (Fig. 1). As many as 40% of individuals with MCI are negative for amyloid beta ($A\beta$) and thus have cognitive impairment due to factors other than AD [8]. It will be important to determine the extent to which demyelination co-occurs with $A\beta$ and/or vascular disease and whether it is evident during the preclinical stage of disease. Application of this methodology to a larger cohort also would permit a more detailed investigation of associations between extent and regionality of demyelination and the degree of cognitive impairment.

Our results in young participants indicated, overall, greater myelin content, *i.e.*, MWF, in comparison to the old unimpaired participants (Fig. 2). This is in good agreement with changes recently observed in healthy aging [34, 47] where it has been shown that myelin content follows an inverted U relationship with age [47]. In addition, we found that increase in MWF was accompanied by increased MTR and decreased T_1 and T_2 , in good agreement with the literature [17–20, 34].

Several methods have been developed for MWF mapping using MRI, reflecting the great importance of this quantity for studies of the central nervous system [48]. Of these, mcDESPOT has emerged as particularly promising due to the possibility of rapid, high-resolution, whole-brain coverage, and the flexibility of the underlying model. However, deriving MWF from mcDESPOT data requires a complex mathematical analysis which is particularly sensitive to noise. We developed the BMC-mcDESPOT method specifically to address this issue [38–40]. BMC-mcDESPOT permits the mapping of MWF in the clinical setting with greatly improved accuracy over previous methods, and we have applied it here to provide the first demonstration of MWF alterations in MCI, AD and VD; this has not previously been demonstrated using any of the available methods for MWF mapping. Furthermore, mcDESPOT also provides a means for stable T_1 and T_2 relaxation time mapping, providing confirmatory indirect information about myelin patterns without the need for additional scans [34, 36]. As with all methods of MWF estimation, BMC-mcDESPOT results are affected by experimental and analytic aspects of data acquisition and analysis [35, 39–41, 49]. Indeed, there is a great deal of current interest in comparing quantitative outcomes from the several available methods for MWF analysis [48, 50]. However, the presence and regionality of myelin loss is remarkably consistent across methodologies.

There are a number of key areas in the study of MCI and dementia that may be illuminated by the availability of accurate and reproducible MWF measurement [17–20]. These include vulnerability of oligodendrocyte metabolism to local blood flow through combined MRI mapping of MWF and implementation of MRI-based flow measurements, the relationship between plaque formation and myelin loss through multi-parametric analysis of combined PET-MRI studies, and the relationship of quantitative myelination status to cognitive and functional outcomes; the latter has been explored in multiple sclerosis (MS) through use of MWF mapping. Finally, we note that oligodendrocytes, the myelin-forming cells of the brain, are particularly rich in iron content [51]. Therefore, a further intriguing possibility is to perform studies using the emerging technique of quantitative susceptibility weighted MRI, which is particularly sensitive to local iron content, in conjunction with MWF mapping, to characterize the interplay of iron deposition and local myelination.

An important limitation of our study is the limited sample size in this initial study, so that no statistical conclusions can be drawn regarding disease status. However, our goal here was to establish the applicability of our MWF mapping method to MCI and AD, to establish consistency with previous findings based on indirect measures [29–33], and to add further evidence for the plausibility of the myelin hypothesis through demonstration of myelination deficits in a small group of subjects with cognitive impairment. As a part of the Baltimore Longitudinal Study of Aging (BLSA), our ongoing work centers on performing statistical and regional analyses on a much larger cohort of subjects.

In this ongoing work, we will test the hypothesis that myelination deficits will correlate in a quantitative fashion with cognitive decline and impairment. Recent resting state functional MRI studies have emphasized the importance of changes in functional network connectivity across the AD spectrum. For example, Jones *et al.* reported altered connectivity in the default mode network along the spectrum of AD from preclinical disease to MCI to AD

[25]. The default mode network hubs of high connectivity are metabolically active regions which also show increased regional A β , even in cognitively normal individuals [52]. It is possible that demyelination underlies changes in altered connectivity which may also impact downstream A β and tau deposition. Ongoing studies in the BLSA neuroimaging program acquire information on inter-regional and network connectivity through resting state functional MRI and diffusion tensor imaging and A β in a subset of individuals. As we acquire additional MWF assessments, we will determine whether demyelination mediates changes in functional connectivity and associated cognitive changes in aging and neurodegenerative disease. We can also directly evaluate the association between A β in default mode regions and demyelination in the fibers connecting those regions. We have expanded the acquisition of MWF studies in the BLSA and current interim results support the robustness of our findings of increased myelination deficits in conjunction with cognitive impairment. Following this validation, extension to other samples such as in the Alzheimer's Disease Neuroimaging Initiative study [53], which includes larger groups of impaired individuals, would be warranted.

In order to amplify the interpretation of these myelination changes as causative, rather than as simple correlates of cognitive impairment, a substantial longitudinal study would be required. One potential design would consist of a study of aging individuals with and without A β as an early sign of accumulation of AD pathology. A temporal relationship between myelination and cognitive changes could then be established in individuals in whom cognitive decline occurs or progresses, and those in whom cognitive status is more stable. Along with these studies, it would be critical to quantify the effects on cognition of interventions aimed at improving myelination, and conversely. Thus, the development and implementation of a stable and accurate MWF protocol, such as presented in this work, may be of substantial value in this undertaking.

We believe that these further studies would lay the foundation for potential use of MWF as an additional biomarker for cognitive decline and dementia, similar to the way in which MRI measurements of myelin have been related to disease progression in multiple sclerosis [22, 54–58]. This would be directly applicable to the design of clinical trials designed to promote myelin stabilization and growth; accurate and stable measurements of the MWF would permit myelination to serve as a new therapeutic target to be correlated with cognitive status, along with markers such as A β and tau [17–20].

Acknowledgments

This work was supported by the Intramural Research Program of the NIH, National Institute on Aging. We gratefully acknowledge the assistance of Dr. Ara Khatchaturian and Dr. Zaven Khatchaturian in defining the overall structure of this manuscript.

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Figure 1.

Parameter maps obtained from MCI, AD or VD subjects. Examples of MWF, MTR, T_2 and T_1 maps obtained from the brains of three old subjects with documented MCI, one subject with documented AD and one subject with documented VD are displayed for a representative slice. White arrows indicate regions exhibiting significant regional demyelination. In these regions, the MWF decrease was accompanied by decreased MTR and increased T_1 and T_2 .

Figure 2. Parameter maps obtained from young or old non-impaired subjects. Examples of MWF, MTR, T_2 and T_1 maps obtained from the brains of three young and three old non-impaired subjects are displayed for a representative slice.