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Theoretical Article

Evidence of demyelination in mild cognitive impairment and dementia using a direct and specific magnetic resonance imaging 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 of myelin.

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

Results: MCI subjects showed decreased MWF compared with old controls. Demyelination was greater in Alzheimer's disease or vascular dementia. As expected, decreased MWF was accompanied by decreased magnetization transfer ratio and increased relaxation times. The young subjects showed greater myelin content than the old subjects.

Discussion: We believe this to be the first demonstration of myelin loss in MCI, Alzheimer's disease, and vascular dementia using a method that provides a quantitative magnetic resonance imaging–based measure of myelin. Our findings add to the emerging evidence that myelination may represent an important biomarker for the pathology of MCI and dementia. This study supports the investigation of the role of myelination in MCI and dementia through use of this quantitative magnetic resonance imaging approach in clinical studies of disease progression, relationship of functional status to myelination status, and therapeutics. Furthermore, 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 noninvasive markers for MCI and presymptomatic 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 β (Aβ) accumulation has been recognized as a hallmark of AD pathology for over 2 decades. The formation of Aβ 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

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pathophysiologic basis for AD and has been supported both by theoretical considerations and various experimental results. For example, removal of Aβ 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 Aβ and tau deposition [7,8]. Furthermore, anti-Aβ 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]. Therefore, 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 et al [17–20], suggests that the breakdown of myelin may promote the deposition of Aβ 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 magnetic resonance (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. Therefore, the emphasis is on the integration of all aspects of the brain architecture and function. Of note, myelin mapping is one of the key components of the magnetic resonance imaging (MRI) sequences used; although indirect measures were performed (see below), this nevertheless highlights the central importance of myelination patterns in current concepts relating the brain structure to cognitive function. We believe that the reliability of further investigations of myelin patterns will be substantially augmented by the use of more advanced metrics for myelination, such as the new approach to myelin water fraction (MWF) which we have developed and applied to cognitively impaired and unimpaired adults in this article. 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 MRI. However, these studies have relied on 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 [34–40] allows for direct measures of myelin through quantification of MWF. In fact, MR-derived MWF correlates with myelin content better than the other indirect myelination markers [41,42]. In addition, using mcDESPOT MRI, Dean et al [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 Aβ pathology. Furthermore, direct correlation of MRI-based MWF mapping and histologic evaluation of myelin has been established [41]. 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.