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Study of Neurodegenerative Diseases with Novel MRI Techniques

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Study of neurodegenerative diseases with novel MRI techniques

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Life is awesome!

ABSTRACT

Neurodegenerative diseases are a heterogeneous group of disorders that are characterized by the progressive degeneration of structure and function of the nervous system. They include diseases such as Alzheimer's disease (AD), multiple sclerosis (MS) and others. The main aims of this thesis were to study functional and/or structural brain changes in AD and MS using novel magnetic resonance imaging (MRI) techniques.

The concentration of β-amyloid$_{1\text{-}42}$ (Aβ42), total tau (T-tau) and tau phosphorylated at position threonine 181 (P-tau$_{181p}$) in cerebrospinal fluid (CSF) may reflect brain pathophysiological processes in AD. We found a positive correlation between functional connectivity within the default mode network (DMN) and the ratio of Aβ42/P-tau$_{181p}$ in sporadic AD (**Paper I**). Furthermore, there were correlations between AD CSF biomarkers and changes of gray matter volume, fractional anisotropy (FA) and mean diffusivity (MD). The majority of brain regions with statistically significant correlation with biomarkers of AD overlapped with the DMN (**Paper II**). These findings implicate that the brain functional connectivity and structure are affected by pathological changes at an early stage in AD. We also found a significantly increased MD in pre-symptomatic mutation carriers (pre-MCs) of AD compared with non-carriers (NCs), and increased MD associated with AD CSF biomarkers (**Paper III**). Similar results were observed both in sporadic and familial AD, which suggests that MD may reflect pathology of early stage AD. Although the exact causes of these changes are difficult to identify, the increased MD may be explained by myelin loss. In MS, myelin loss is one of the characteristic events of the pathological process. By combining susceptibility-weighted MRI with analysis of the T_2^* decay curves, we were able to characterize and quantify myelin loss (**Paper IV**).

In conclusion, pathological changes in AD and MS could be detected by novel MRI techniques. This suggests that these techniques may also be helpful in further understanding pathology in other neurodegenerative diseases. As non-invasive tools, these novel MRI techniques are possible to screen individuals susceptible to and/or manifesting early neurodegeneration.

LIST OF PUBLICATIONS

I. **XIAOZHEN LI**, Tie-Qiang Li, Niels Andreasen, Maria Kristoffersen Wiberg, Eric Westman, Lars-Olof Wahlund.
Ratio of Aβ42/P-tau$_{181p}$ in CSF is associated with aberrant default mode network in AD.
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II. **XIAOZHEN LI**, Tie-Qiang Li, Niels Andreasen, Maria Kristoffersen Wiberg, Eric Westman, Lars-Olof Wahlund.
The association between biomarkers in cerebrospinal fluid and structural changes in the brain in patients with Alzheimer's disease.
J Intern Med. 2014; 275(4): 418-27.

III. **XIAOZHEN LI**, Eric Westman, Anne Kinhult Ståhlbom, Steinunn Thordardottir, Ove Almkvist, Kaj Blennow, Lars-Olof Wahlund, Caroline Graff
White matter changes in familial Alzheimer's Disease.
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IV. **XIAOZHEN LI**, Peter van Gelderen, Pascal Sati, Jacco A. de Zwart, Daniel S. Reich, Jeff H. Duyn
Detection of demyelination in multiple sclerosis by analysis of T_2^* relaxation at 7T.
Neuroimage Clin. 2015; 7:709-714

CONTENTS

LIST OF ABBREVIATIONS

Aβ	Amyloid β
AAO	Average age at symptom onset
AD	Alzheimer's disease
AP	Amyloid plaque
APOE	Apolipoprotein E gene
APP	Amyloid precursor protein
CSF	Cerebrospinal fluid
DMN	Default mode network
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
EDSS	Expanded disability status scale
FA	Fractional anisotropy
FAD	Familial Alzheimer's disease
FLAIR	Fluid-attenuated inversion recovery imaging
GM	Gray matter
MC	Mutation carrier
MCI	Mild cognitive impairment
MD	Mean diffusivity
mGRE	Multi-gradient-echo imaging
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NAWM	Normal appearing white matter
NC	Non-carrier
NFT	Neurofibrillary tangle
OD	Other dementia
PD	Parkinson's disease
pre-MC	Pre-symptomatic mutation carrier
pre-gad T_1-w	Pre-gadolinium T_1-weighted imaging
post-gad T_1-w	Post-gadolinium T_1-weighted imaging
PSEN	Presenilin
P-tau$_{181P}$	Tau phosphorylated at position threonine 181
RRMS	Relapsing remitting multiple sclerosis
rs-fMRI	Resting-state functional magnetic resonance imaging
SCI	Subject cognitive impairment
TE	Echo time
TR	Repetition time
T-tau	Total tau
T_1-w	T_1-weighted imaging
T_2-w	T_2-weighted imaging
VBM	Voxel-based morphometry
WM	White matter

1 INTRODUCTION

1.1 Neurodegenerative diseases

Neurodegenerative diseases are traditionally defined as disorders with progressive loss of neurons in distinct anatomical distribution, and accordingly different clinical phenotypes (Kovacs and Budka, 2010). This includes diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis and others. These diseases are relatively common, especially AD, PD and MS.

Neurodegenerative diseases occur when neurons in the brain and spinal cord begin to deteriorate. Changes in these cells cause them to function abnormally and eventually result in the death of the cells. These diseases generally begin slowly but inexorably cause progressive neuronal degeneration and result in disability or death. An individual may first experience relatively mild problems. But as large numbers of neurons die, symptoms progressively worsen. In some cases, patients lose the general function in their life, the ability to think clearly and/or walk independently. Ultimately, many of these diseases are fatal.

Traditionally, different diagnoses of neurodegenerative diseases, such as AD and MS, have been thought to present with different symptoms and arise through different disease processes. However, while many different forms of neurodegenerative diseases are recognized, the lines that separate one from another are often unclear. For instance, symptoms such as motor impairment and memory loss may occur in many different types of neurodegenerative disease. It is therefore difficult to reach an accurate diagnosis before the patient reaches a more advanced stage of the disease.

Neuropathological evaluation, which is often considered the gold standard of diagnosis, can also show marked overlap between the syndromes of age-related cognitive and motor impairment. Upon histological examination, the brains of individuals with different neurodegenerative disorders show characteristic cellular and tissue abnormalities. However, it has been shown that the brains of individuals with one form of neurodegeneration could also have the pathological markers of another (Schneider et al., 2007). Co-pathology of amyloid β (Aβ) and tau is present in several neurodegenerative diseases, including AD, PD, and some cases of multiple

system atrophy (Kovacs and Budka, 2010). Moreover, the presence of soluble oligomers, common to most amyloids, in MS brains has been demonstrated (David and Tayebi, 2014).

Neurodegenerative diseases share several common features with respect to clinical course, pathology, and molecular mechanisms. However, the mechanisms responsible for their pathologies are not completely understood, and there are currently no effective preventive therapies. Some studies have demonstrated that these disorders are characterized by a pre-symptomatic phase, likely lasting years, during which neuronal degeneration is occurring but before clinical symptoms appear (DeKosky and Marek, 2003). Thus, there is a need for the development of non-invasive detection tools to identify individuals at early stage, or even during the preclinical period. Moreover, early detection of neurodegenerative diseases would be beneficial in understanding the pathologies mechanism and progression from the very beginning, and would enable preventive and more effective treatment of the patients.

1.2 Alzheimer's disease

Originally reported by the German psychiatrist Alois Alzheimer in 1907, AD has become the most common neurodegenerative disease worldwide. In 2010, 35.6 million persons suffered from dementia worldwide, most from AD. It has been shown that the prevalence and incidence of dementia increases exponentially between the ages of 65 and 85, doubling in every five-year age group. Based on these numbers, it has been projected that the number of persons with dementia will reach 65.7 million in 2030, and 115.4 million in 2050 (Alzheimer's Disease International, 2009).

AD is clinically characterized by progressive cognitive impairment decline leading to complete dependence on care within some years after clinical diagnosis. Disease onset is typically characterized by loss of memory for recent events, but later develops into a more severe disorder including: visuospatial problems, dysphagia, anemia, orientation difficulties, anxiousness, irritability, and severe cognitive and intellectual disturbances. Eventually, patients no longer function normally. Mild cognitive impairment (MCI) is recognized as the prodromal stage of AD, representing a transitional period between normal aging and AD (Petersen et al., 1997; Albert et al., 2011). Subjects with MCI developed dementia, usually AD, at a rate of 10% to

15% per year, which is much higher than in age-matched controls (1% to 2% per year) (Petersen et al., 1997). More than half of MCI patients progress to dementia within three to five years (Petersen et al., 2001). There is evidence indicating that subjective cognitive impairment (SCI), also referred to as subjective memory complaints or subjective cognitive decline, is a stage prior to MCI in the eventual development of AD dementia (Reisberg and Gauthier, 2008; Jessen et al., 2014). A probable duration of 15 years for the SCI stage has been supported by a longitudinal study (Glodzik-Sobanska et al., 2007).

Two abnormal protein aggregates characterize AD pathologically. These proteinopathies are the basis of the well-known amyloid plaques (APs) and neurofibrillary tangles (NFTs) (Jack, 2012). APs form in the extracellular space, while NFTs are intracellular aggregates, containing Aβ and hyperphosphorylated tau, respectively (Blennow et al., 2006). Under physiological conditions, Aβ peptides of 39-43 amino acids are the peptide products of the larger amyloid precursor protein, with Aβ40 being by far the most abundant (Masters et al., 1985; Iwatsubo et al., 1994). Aβ42 aggregates more readily than other species into soluble oligomers, and insoluble fibrils characterized by a β-pleated sheet conformation, eventually forming the AD-typical plaques (Iwatsubo et al., 1994). In amyloid cascade hypothesis of AD, an imbalance between the production and clearance of Aβ in the brain is the initiating event, ultimately leading to dementia (Hardy and Selkoe, 2002). Tau is a phosphoprotein and component of the cytoskeletal microtubule system. In AD, tau becomes hyperphosphorylated, disassociates from microtubules, assumes a paired helical filament configuration, and forms insoluble NFTs inside neurons (Jack, 2012).

Progression of APs and NFTs pathology throughout the brain (a process that has been called ‘spreading’) generally proceeds in a particular manner. APs develop in poorly myelinated areas of the basal neocortex, then spread into adjoining areas and the hippocampus, and eventually infiltrate all cortical areas, including densely myelinated primary fields of the neocortex (Braak and Braak, 1997). The NFTs pathologic process of AD begins in the transentorhinal area and progresses to the hippocampus, then to paralimbic and adjacent medial-basal temporal cortex, to neo-cortical association areas, and lastly to primary sensorimotor and visual areas (Braak and Braak, 1991). Such brain changes occur decades before the onset of dementia, leading

to progressive loss of functions, metabolic alterations and structural changes in the brain (Morris and Price, 2001).

Several susceptibility genes have been identified in connection with AD. The most consistently associated is the ε4 allele of the apolipoprotein E gene (*APOE*) (Bertram and Tanzi, 2012). *APOE* exists in three isoforms ε2, ε3, and ε4. *APOE* ε4 allele implies a three-fold increase in risk of AD in heterozygotes and 15 times in homozygotes (Farrer et al., 1997), whereas the *APOE* ε2 allele decreases risk (Albert et al., 2011). *APOE* ε4 may affect AD pathogenesis by promoting deposition of the Aβ and formation of plaque (Holtzman et al., 2000).

Genetic factors are important in all forms of AD but especially in familial AD (FAD). They are characterized by early-onset, before 60 years of age, a strong familial aggregation, which accounts for only about 1% to 6% of all AD cases (Alonso Vilatela et al., 2012). Similar to sporadic AD, most FAD cases present with an insidious onset of episodic memory difficulties followed by other cognitive impairments (Bateman et al., 2011). FAD exhibits the same pathological hallmarks as sporadic AD, including APs and NFTs (Shepherd et al., 2009). Currently, pathogenic mutations in three genes have been identified: amyloid precursor protein (*APP)*, presenilin 1 (*PSEN1*), and *PSEN2* (Bertram et al., 2010), which are all involved in the Aβ pathway (Wu et al., 2012; Wanngren et al., 2014). *PSEN1* mutations are responsible for nearly 75-80% of genotype-positive families in a mutation, *APP* and *PSEN2* mutations are responsible for 15-20% and less than 5%, respectively (Wu et al., 2012). *PSEN1* mutation carriers (MCs) have an average age of symptom onset (AAO) in the early 40s, ranging from 24 to 65 years. While *APP* MCs have a later AAO, typically in the 50s and ranging from 45 to 60 years; and *PSEN2* mutations have a wide range of onset with some relatively late-onset cases (Bateman et al., 2011). Due to nearly 100% penetrance in FAD MCs, serial neuroimaging or CSF examination in the early stage of the MCs provides an opportunity to identify early biomarkers of FAD that can be used to track disease progression from the pre-symptomatic stage through to dementia (Wu et al., 2012).

The brain is in direct contact with the cerebrospinal fluid (CSF). Biochemical changes that reflect pathophysiologic processes in the brain are reflected in the CSF (Tapiola et al., 2009; Engelborghs and Bastard, 2012). Concentrations of Aβ42, total tau (T-

tau) and tau phosphorylated at position threonine 181 (P-tau$_{181p}$) in CSF may be sensitive biomarkers of incipient APs and NFTs formation in AD. Both Aβ42 and tau proteins of CSF can be reliably measured (Vandermeeren et al., 1993; Vanmechelen et al., 2000). It has been reported that CSF Aβ42 concentrations are decreased, while T-tau and P-tau$_{181p}$ concentrations are increased in AD patients, even in MCI and SCI patients (Blennow et al., 2006; Hansson et al., 2006; Visser et al., 2009). Furthermore, decreased Aβ42 and increased P-tau$_{181p}$ and T-tau in CSF have been found in *APP* and *PSEN1* MCs (Ringman et al., 2008; Wu et al., 2012). CSF Aβ42 is reduced in AD which may be associated with the deposition of the peptide in plaques with lower concentrations diffusing to the CSF. CSF T-tau and P-tau$_{181p}$ are increased probably as a result of neuronal and axonal degeneration (Blennow et al., 2006). The correlation of these CSF biomarkers and AD pathological hallmarks has also been confirmed in a neuropathological study. Seppälä et al (Seppälä et al., 2012) demonstrated that APs and hyperphosphorylated tau in cortical brain biopsies were reflected by low CSF Aβ42 and high CSF T-tau and P-tau$_{181P}$ levels, respectively. The diagnostic accuracy of the CSF biomarkers has been assessed in some studies (Ferreira et al., 2014a). The diagnostic sensitivities for CSF Aβ42 and T-tau in AD against cognitively normal elderly people were 80% and 82%, and the specificities were 82% and 90% respectively. The addition of CSF P-tau$_{181P}$ increases the ability to differentiate AD from other dementias (OD), reaching specificity around 80%. Moreover, concentrations of CSF Aβ42, T-tau and P-tau$_{181P}$ also showed strong association with future development of AD in patients with MCI (Hansson et al., 2006). The combination of Aβ42 and P-tau$_{181p}$ was the most predictive assay for AD among MCI patients (Herukka et al., 2005; Ferreira et al., 2014b).

1.3 Multiple sclerosis

More than 100 years have passed since Jean-Martin Charcot first described MS as ‘sclerose en plaques’ (Makris et al., 2013). MS is one of the most common neurological disorders and causes of disability in young adults. Globally, the median estimated prevalence of MS is 30 per 100 000 (with a range of 5–80), depending on the region, and is highest in Europe (80 per 100 000), Eastern Mediterranean (14.9) and the Americas (8.3). An estimated 2.6 million worldwide were diagnosed with MS, of which approximately 630 000 were in Europe and 520 000 in the Americas, (World Health Organization, 2008).

The main feature of MS is a variable neurological dysfunction showing characteristic relapses and remissions without any specific pattern. Four main subtypes are defined according to the natural history of the disease: relapsing remitting MS (RRMS), which is the most common, including almost 85% of the patients affected, primary progressive MS, progressive relapsing MS, and secondary progressive MS (**Figure 1**) (Noseworthy et al., 2000). Symptoms may involve the entire ascending or descending axons and can sometimes predominantly affect the spinal cord and optic nerves (Compston and Coles, 2002). The most common clinical signs include sensory disturbance, unilateral optic neuritis, limb weakness, clumsiness and cognitive dysfunction (Noseworthy et al., 2000). The rating of the neurologic impairment in MS is mostly evaluated using the expanded disability status scale (EDSS) (Kurtzke, 1983), which is also a useful tool for predicting future disability (Chruzander et al., 2013).

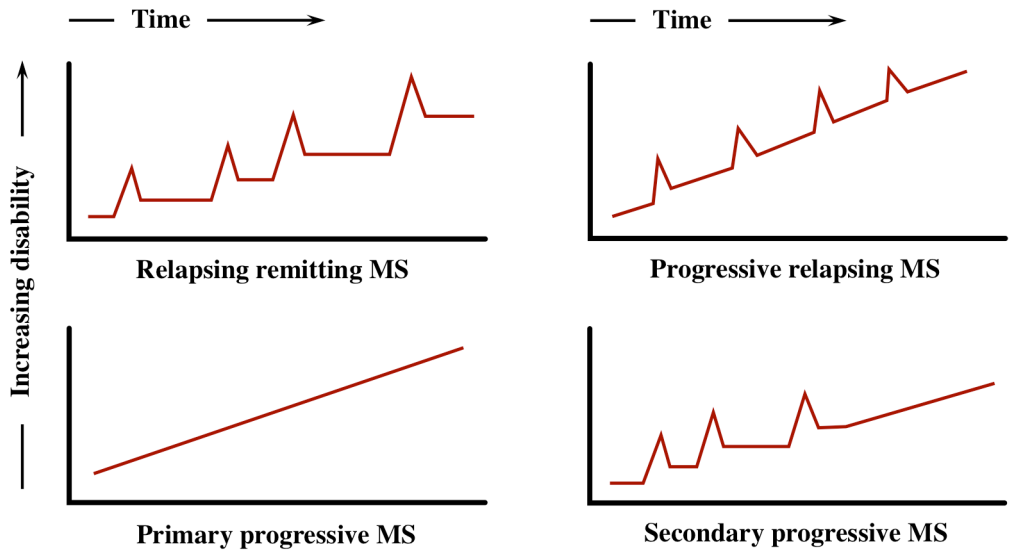

Figure 1. Progression of MS subtypes.

MS is generally believed to be an immune-mediated disorder of the central nervous system characterized by extensive myelin loss (Haines et al., 2011). Focal lesions are the diagnostic hallmark of MS pathology, which consist of demyelination, inflammation, scar formation and variable axonal destruction (Pittock and Lucchinetti, 2007). The cores of the lesions are filled with a central vein that is surrounded by inflammatory components and demyelination, which occur in the

white matter (WM) and gray matter (GM) in the brain and spinal cord (Lassmann et al., 2012). MS lesions can be characterized as active and inactive (Lassmann et al., 1998). Active lesions are heavily infiltrated by macrophages containing myelin debris that are often closely associated with the disintegrating myelin sheath, while the chronic inactive MS lesion is a hypocellular plaque with no evidence of active myelin breakdown. Fibrillary gliosis is prominent and axonal density is often markedly reduced in chronic inactive plaque (Pittock and Lucchinetti, 2007).

Several mechanisms have been proposed to explain the pathogenesis of progressive MS (Lassmann et al., 2012). One of these mechanisms postulates that brain damage is driven by inflammatory processes. Another potential mechanism suggests that MS starts as an inflammatory disease and after several years of chronic inflammation, neurodegeneration, which is independent of inflammatory response, results in disease progression. Finally, others have suggested that MS might be primarily a neurodegenerative disease, the progression of which is modified or amplified by inflammation in the early disease stage. Relapses are considered as recurrent episodes of inflammation and demyelination, often accompanied by axonal injury. Remission of symptoms after an attack may relate to resolution of inflammation and/or remyelination (Pittock and Lucchinetti, 2007). Unfortunately, neither clinical nor pathologic features clearly predict clinical course or outcome.

It is still not known what causes MS, but it is believed that this disease occurs as a result of both environmental and genetic factors. Genetic studies have identified many MS risk-gene regions (Katsavos and Anagnostouli, 2013). However, the distribution of MS cannot be explained on the basis of population genetics alone (Compston and Coles, 2002). In other words, it is likely that the risk genes contribute or indirectly influence interactions with the currently known environmental risk factors, including decreased sun exposure, vitamin D deficiency, viral infections (particularly Epstein-Barr virus), and smoking (Burrell et al., 2011).

Information on the oligoclonal IgG bands in CSF is useful for MS diagnosis. The diagnostic sensitivity is high (>90%), while the specificity among inflammatory disorders of the central nervous system is only around 35% (Katsavos and Anagnostouli, 2013), and could not differentiate subtypes of MS (Stangel et al., 2013). Some other biomarkers for MS include osteopontin, TNF-alpha, and various

cytokines, and have been reported with different sensitivity and specificity (Katsavos and Anagnostouli, 2013). So far, none of the existing biomarkers can fully reflect the immensity of diverse MS pathogenic mechanisms creating a unique result.

1.4 Magnetic resonance imaging

In the past two decades, magnetic resonance imaging (MRI) has been playing an increasingly important role in the study and clinical diagnosis of neurodegenerative diseases.

MRI is a non-invasive method that uses the resonance of protons to create a signal, which is then processed to generate images. Hydrogen atoms are the most common protons to create the signal and are excited by a radiofrequency pulse with a specific frequency, the same frequency as the protons. When the radiofrequency is switched off, the excited protons emit energy in a radio frequency signal as they return to their original state; this process is called relaxation. The relaxation starts both longitudinally and transversely. Longitudinal relaxation, known as spin-lattice relaxation, refers to the process in which the excited protons return the energy to the surroundings. While transverse relaxation, also known as spin-spin relaxation, is observed due to the interactions of excited protons dephasing from each other. The relaxation rates are characterized by two relaxation times, T_1 and T_2, respectively. In real systems, however, the transverse relaxation decays much faster than would be predicted by natural atomic mechanisms; this rate is called as T_2^*, which is a combination of "true" T_2 relaxation and relaxation caused by magnetic field inhomogeneity (Chavhan et al., 2009). Variations in proton relaxation times are the primary cause of contrast in MRI; however proton density is also an important factor. Besides these, the diffusion coefficient is widely used to generate contrast based on the physical properties of water molecules, which represents the thermal (or Brownian) motion of water molecules (Mori and Zhang, 2006). The images generated with different contrasts are called T_1-weighted imaging (T_1-w), T_2-weighted imaging (T_2-w), T_2^*-weighted imaging (T_2^*-w), proton density and diffusion-weighted imaging (DWI) respectively.

Novel MRI techniques from structure to function are widely used to investigate the brain abnormalities associating with vulnerability to develop neurodegenerative diseases and their progression.

1.4.1 MRI techniques

1.4.1.1 Resting-state functional MRI

Resting-state functional MRI (rs-fMRI) is a type of specialized MRI scan with a fast T_2^* sensitive sequence that uses blood-oxygen-level-dependent contrast to measure the hemodynamic response (change in blood flow) related to spontaneous activity in the brain at resting state. The synchrony between low frequency fluctuations in signal intensity of rs-fMRI data has been used as a measure of functional connectivity in spatially separated brain regions (Biswal et al., 1997). Although the precise physiologic mechanism measured with functional connectivity is not fully understood, there is much evidence in support of the notion that the coordinated activity changes in the brain are related to the establishment or maintenance of synaptic connections between neurons (Leopold and Maier, 2012). rs-fMRI has been successfully used to map connectivity between distant brain regions that are functionally related (Greicius et al., 2004).

1.4.1.2 Voxel-based morphometry

Voxel-based morphometry (VBM) is a neuroimaging analysis technique that compares the local intensity of brain tissue at every voxel to assess structural characteristics such as volume or density in neuroanatomy. VBM consists of spatially normalizing high-resolution T_1-w from every subject in the study to the same space (standard or study template), which gets rid of most of the large differences in brain anatomy among people. Then, the spatially normalized image is segmented into the GM, WM and CSF, and smoothed so that each voxel represents the average of itself and its neighbors. Finally, the image volume is compared across brains at every voxel. Compared to traditional manually morphometric methods, such as the manual delineation of specific regions of interest, VBM approach is not biased to one particular structure and gives an comprehensive assessment of anatomical differences throughout the brain (Ashburner and Friston, 2000).

1.4.1.3 Diffusion tensor imaging

Compared to morphometric methods that measure the macrostructural damage of disease (e.g. VBM), diffusion tensor imaging (DTI) measurements evaluate the microstructural damage of disease. DTI is a quantitative MRI technique that measures the movement of water within the tissue microstructure (Chua et al., 2008). The two most common measurements are fractional anisotropy (FA) and mean diffusivity (MD). FA is a measure of anisotropic water diffusion, and reflects the degree of directionality of cellular structures within the fiber tracts and therefore their structural integrity. In a purely isotropic media, FA would be 0, and with increasing anisotropy the value tends towards 1. MD provides an index of average diffusional motions of water molecules. The loss of macromolecular tissue content results in an increase in free water diffusion and consequentially increased MD. The changes in FA and MD can, therefore, be related back to abnormalities within the cellular microstructure to provide information about their structural integrity.

1.4.1.4 Separation of T_2^* relaxation components

Multi-gradient-echo imaging (mGRE) for mapping the T_2^* relaxation decay curve has been proposed as a new way to obtain cellular compartment-specific information in WM (Du et al., 2007; Hwang et al., 2010; van Gelderen et al., 2012; Sati et al., 2013). Since the myelin sheath acts as a water diffusion-restricting barrier due to its multilayer structure, it is indeed generally accepted that three major distinct water pools can be distinguished in WM (Lancaster et al., 2003; Laule et al., 2004; Andrews et al., 2005; MacKay et al., 2006): water between the myelin layers (or myelin water), interstitial water (or extracellular water) and intra-axonal water. Under the assumption of a slow-exchange process between these pools, one would observe multi-exponential T_2^* decay as a function of echo time (TE) for myelin containing tissue (van Gelderen et al., 2012). Therefore, information about the relative sizes of myelin water and axonal water pools could be gained from fitting a three-component model to the T_2^* relaxation curve. This could provide new insights into myelin breakdown, axonal injury and degenerative processes.

1.4.2 MRI in AD

Due to the uncertainties associated with the clinical diagnosis, a variety of novel imaging modalities including structural, functional, and molecular neuroimaging

techniques have been adopted for identifying specific diagnostic patterns in individuals who may be at risk of AD.

A progressive accumulation of amyloid and NFTs in the brain tissue eventually result in neuronal death and diffuse brain atrophy (**Figure 2**) (Anand et al., 2012), which can be measured by MRI. VBM has been extensively used to measure morphological changes in AD studies during the past two decades (Li and Wahlund, 2011). The hippocampus and the entorhinal cortex have been identified as suffering from the most severe atrophy in AD (Li and Wahlund, 2011). Atrophy in the medial temporal lobe can predict the development of AD and the rate of progression from MCI to AD (Korf et al., 2004; Devanand et al., 2007). Furthermore, significant GM atrophy in the temporal lobe, precuneus and cingulate gyrus were observed in symptomatic MCs, compared with non-carriers (NCs) (Cash et al., 2013). Longitudinal studies have demonstrated bilateral hippocampal atrophy in MCs before the appearance of symptoms (Fox et al., 1996). Hippocampal volumes of MCs were smaller than those of age- and sex-matched control subjects at each stage, but the differences were not statistically significant until the MCI stage (Ridha et al., 2006).

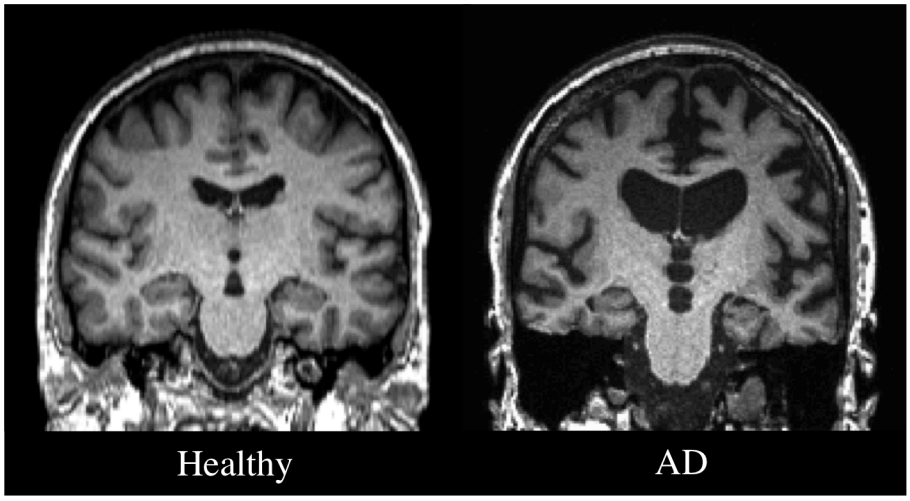

Figure 2. Brain atrophy in AD.

In addition to brain atrophy, DTI measurements indicating cerebral damage are commonly found in patients with AD and MCI. Altered MD and FA have been reported in many different regions. During neurodegeneration, cell loss leads to increased diffusion of water molecules that can be quantified by elevated MD. Likewise, processes that lead to disturbances of WM structural integrity can be

expressed by decreased FA, indicating a disruption of cerebral integrity in the brain (Fellgiebel et al., 2004). The most commonly reported regions of DTI alterations are the temporal lobes, splenium of corpus callosum and the posterior cingulate area (Stebbins and Murphy, 2009; Sexton et al., 2011). DTI measurements in the hippocampus are also reliable and precise (Müller et al., 2006) and it has been shown that the MD increases in the hippocampus with increasing AD disease severity (Cherubini et al., 2010). The alteration pattern in individuals with MCI is similar to that seen in patients with AD, but is not as extensive. Decreased FA of the fornix in pre-MCs and early symptomatic MCs were reported by Ringman et al (Ringman et al., 2007). Moreover, Ryan et al (Ryan et al., 2013) found widespread decreased FA and increased MD in symptomatic MCs, but no significant differences in FA and MD were seen for pre-MCs compared with control subjects.

As a biomarker of synaptic dysfunction, rs-fMRI has been widely used in AD studies during the past years and may demonstrate abnormality very early in AD (Sperling et al., 2011). The rs-fMRI studies for AD mainly focused on a specific set of brain regions within the default mode network (DMN) (Raichle et al., 2001). The principal regions involved in the DMN are the medial prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex/precuneus and medial temporal regions (i.e., hippocampal and parahippocampal gyri). This network is active during rest and deactivated when individuals are engaged in a broad range of cognitive tasks and it is believed to support a default mode activity of the human brain (Buckner et al., 2008). The link between DMN and episodic memory is well established. It is known that retrieval of episodic memories, whether internally or externally cued, relies on DMN (Huijbers et al., 2011). Activation and deactivation patterns within the DMN have been found to predict episodic memory performance (Daselaar et al., 2009). Altered connectivity within the DMN in AD and MCI has also been reported in many studies (Greicius et al., 2004; Wang et al., 2007; Bai et al., 2008; Jones et al., 2011; Petrella et al., 2011). The most frequent and consistent finding in both AD and MCI is decreased resting state connectivity in the DMN, particularly in the posterior cingulate cortex/precuneus and hippocampus, and disruption of DMN connectivity to other brain regions (Krajcovicova et al., 2014). Moreover, the decreased functional connectivity in the DMN is associated with AD progression (Zhang et al., 2010; Petrella et al., 2011).

1.4.3 MRI in MS

MRI was formally integrated into the MS diagnostic criteria in 2000 (McDonald et al., 2001), and suggested for monitoring disease evolution and treatment efficacy. On MRI, MS plaques are commonly seen as multiple focal lesions with intermediate to low signal on T_1-w and high signal on T_2-w / fluid-attenuated inversion recovery imaging (FLAIR) (**Figure 3**). Typical MS lesions are ovoid-shaped with long-axis oriented perpendicular to the ventricular surface. Characteristic locations include periventricular white matter, corpus callosum, juxtacortical area, and brainstem (Barkhof et al., 1997). Inflammation in acute demyelinating MS lesions causes increased blood-brain barrier permeability. This leads to contrast enhancement on post-gadolinium T_1-weighted imaging (post-gad T_1-w), which is conventionally included in MRI acquisition protocols for MS.

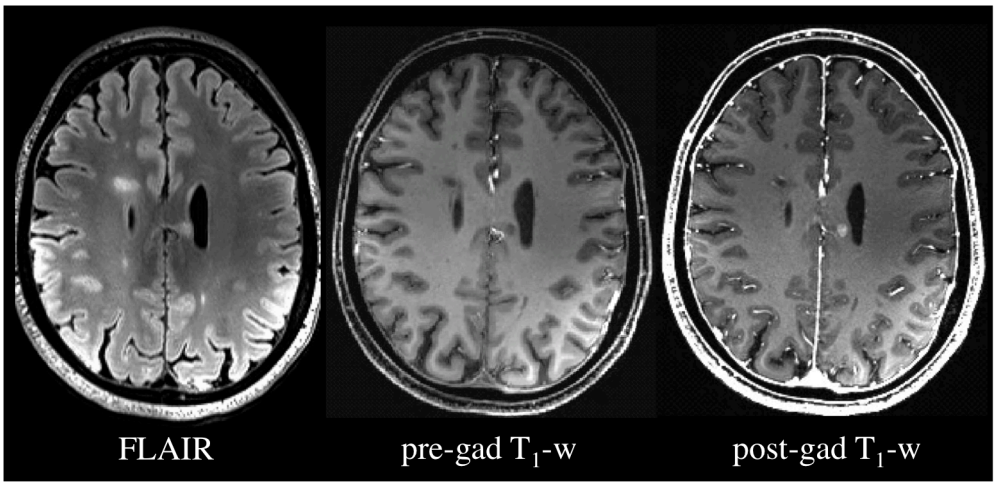

Figure 3. MS lesions on MRI.

Although useful in the diagnosis and management of MS, conventional imaging has several limitations. Lesions are nonspecific, and can reflect areas of inflammation, demyelination, ischemia, edema, cell loss, or gliosis. Meanwhile, numerous studies have attempted to more specifically assess the demyelination process occurring in MS by measuring indirectly the local myelin content using various MR techniques, such as DTI, magnetization transfer imaging, and T_2-based myelin water imaging (Laule et al., 2007). The separation of T_2 relaxation components has been used to measure the amount of water trapped between the myelin layers, which is generally considered to reflect brain myelin content. This is based on the fact that the diffusion-restricting properties of myelin lead to distinct T_2 values for water between the myelin layers (or myelin water), intra-axonal water, and interstitial water (or extracellular water), with

the myelin water pool having the shortest T_2 (MacKay et al., 1994; Lancaster et al., 2003; Laule et al., 2004; Andrews et al., 2005; MacKay et al., 2006). Decreases in the amount of myelin water in MS lesions have been reported by a number of studies (MacKay et al., 1994; Vavasour et al., 1998; Laule et al., 2004). Furthermore, absence of myelin water signal was also found in chronic demyelinated MS lesions (Moore et al., 2000). Although promising, this myelin water measurement method generally suffers from long acquisition time, is limited to low field strength MRI (due to associated tissue heating), and has limited specificity to myelin water. One very recent and particularly promising technique to measure myelin associated water is the use of T_2^* contrast (van Gelderen et al., 2012; Sati et al., 2013). Similar to the T_2 based methods, myelin associated water can be identified based on its short T_2^*, allowing it to be separated from axonal and interstitial water. In addition, the frequency information available with T_2^* contrast, and not with T_2 contrast, improves the discrimination between compartments due to their different frequency shifts. Furthermore, T_2^* based techniques can be applied at high field, where they provide higher resolution and contrast. Preliminary results obtained with this technique in humans suggest that identification of myelin water, and possibly a distinction between axonal and interstitial water, is feasible and may have a clinical impact for demyelinating diseases such as MS (Sati et al., 2013).

2 AIMS OF THE STUDIES

The general aims of this thesis were to study structural and functional brain changes in AD and MS, and the underlying biology by using multiple novel MRI techniques, alone or combined. The specific aims of each study were:

Paper I

To study the correlation of pathological changes reflected by CSF biomarkers and abnormal functional connectivity extracted from rs-fMRI measurements in AD.

Paper II

To determine the relationship of CSF biomarkers and brain structural changes detected by VBM and DTI in AD.

Paper III

To investigate preclinical structural brain changes using VBM and DTI in FAD, and in relation to CSF biomarkers.

Paper IV

To evaluate the benefits of T_2^* based myelin water imaging for the detection of demyelination in MS and determine the relationship between demyelination and observed changes in myelin, interstitial and axonal water in MS lesions.

3 SUBJECTS AND METHODS

3.1 Ethical approval

All studies were conducted according to the Declaration of Helsinki and subsequent revisions. The studies reported in papers I, II and III were approved by the Regional Ethics Committee of Stockholm, Sweden. Paper IV was conducted under an institutional review board-approved natural history protocol at the National Institutes of Health in Bethesda, USA.

3.2 Subjects

The participants of papers I and II were recruited from the Memory Clinic at the University Hospital of Karolinska Huddinge, in Stockholm, Sweden. The subjects of paper III were from four families with different mutations in *APP* or *PSEN1*. The clinical routine examinations generally involved physical examination, evaluation of neurological and psychiatric status, MMSE testing, and detailed neuropsychological assessment, blood and CSF sampling and *APOE* genotyping. All subjects underwent MRI exam on a Siemens whole-body clinical MRI 3T scanner (Magnetom Trio, Erlangen, Germany). AD and OD were clinically diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, fourth Edition/International Classification of Diseases, 10th revision (DSMIV/ICD-10) criteria. MCI was defined using Winblad et al criteria (Winblad et al., 2004). Patients categorized as SCI had cognitive memory complaints but without impairment in objective cognitive tasks (Reisberg and Gauthier, 2008).

The MS patients of paper IV were recruited from the National Institutes of Health in Bethesda, USA. Experienced MS clinicians determined disability according to the Expanded Disability Status Scale (EDSS) and obtained clinical data. All MRI were performed on a 7T human MRI scanner (Siemens, Erlangen, Germany).

All subjects or their caregivers provided written informed consent to participate in the study.

3.3 Paper I

A total of 97 subjects were included in this study (**Table 1**). All participants underwent lumbar puncture to measure the levels of CSF Aβ42, T-tau and P-tau$_{181p}$. All CSF samples were analyzed at Karolinska University Hospital Huddinge.

Table 1. Demographics.

	AD (n=21)	MCI (n=36)	OD (n=17)	SCI (n=23)
Age (y)	65.6±7.1	60.4±9.2	59.3±8.1	57.6±9.1
Gender (M/F)	8/13	17/19	12/5	9/14
MMSE	22.3±5.2	26.1±3.2	23.0±4.0	27.7±2.4
Aβ42 (pg/mL)	483.8±130.8	841.7±352.1	935.4±258.8	1101.0±304.3
T-tau (pg/mL)	634.7±275.9	356.8±197.8	248.5±103.3	276.7±122.4
P-tau$_{181p}$(pg/mL)	88.9±32.9	58.8±24.2	43.8±14.2	51.8±19.4
Aβ42/P-tau$_{181p}$	6.6±4.5	18.0±11.0	24.2±10.4	22.9±6.4

The MRI protocol included a high-resolution sagittal 3D T_1-w and rs-fMRI. The main acquisition parameters of rs-fMRI included: repetition time (TR)/TE = 1600/35 ms, 400 time frames of gradient-recalled echo planar imaging, and 42 contiguous oblique slices of 4mm thick, and measurements lasted 10min and 30s. During the acquisition of rs-fMRI, the subjects were instructed to close their eyes, not to think of anything in particular and not to fall asleep.

T_1-w images were segmented into GM, WM and CSF, and co-registered to the brain template from Montreal Neurological Institute using a VBM protocol with FSL (FMRIB Software Library, http://www.fmrib. ox.ac.uk/fsl/). After pre-processing, the individual DMN map was extracted from rs-fMRI and entered into a voxel-wise statistical test to determine the correlation with the ratio of Aβ42/P-tau$_{181p}$, controlled by age, gender and GM intensity map. The correlation between CSF ratio of Aβ42/P-tau$_{181p}$ and individual average Z-scores of the cluster with statistical significance was tested both for AD, MCI, SCI subjects in total and separately adjusted for age and gender.

3.4 Paper II

Twenty-one patients with AD, 35 MCI and 22 SCI from the same cohort as study I were studied (**Table 2**).

DTI was performed using a spin-echo echo planar imaging sequence with the

following acquisition parameters: TR/TE = 5200/91 ms, 42 axial slices (3.6 mm thick), in-plane voxel size 2×2 mm^2 and 30 orientations for the diffusion-sensitizing gradient pulses at a b-value of 1000 s/mm^2.

Table 2. Demographics.

	AD (n=21)	MCI (n=35)	SCI (n=22)
Age (years)	65.6±7.1	60.3±9.4	56.6±8.1
Gender (M/F)	8/13	17/18	8/14
MMSE score	22.3±5.2	26.4±2.8	27.6±2.5
Aβ42 (pg/mL)	483.8±130.8	826.1±344.3	1089.2±306.0
P-tau_{181p} (pg/mL)	88.9±32.9	58.8±24.5	51.8±19.8
T-tau (pg/mL)	634.7±275.9	357.3±200.7	277.1±125.3

GM intensity map was segmented from T_1-w as in Study I. FA and MD maps were generated from DTI on FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/) as well. GM intensity, FA and MD maps were entered into a voxel-wise statistical analysis to calculate the correlation with CSF Aβ42, T-tau and P-tau_{181p} respectively, adjusted for age and gender. For GM intensity maps, we also added intracranial volume as a covariate. Then the partial correlations between CSF biomarkers and total GM volume, mean FA and MD values of regions with statistical significance were tested both for AD, MCI, SCI subjects in total and separately, adjusted for age and gender. Similar to the voxel-wise analysis, intracranial volume was included as a covariate for GM volume.

3.5 Paper III

A total of 30 subjects, including 10 MCs and 20 non-carriers (NCs) were included in the study. The AAO for each family was 54, 56, 52 and 36 years, respectively. Neither the participants nor the investigators were aware of the mutation status of the family members during the period of their participation in the study. One MC was diagnosed with AD, and two MCs with MCI.

Eight MCs and 13 NCs underwent a lumbar puncture to measure CSF biomarkers. CSF samples were not available for two pre-symptomatic MCs (pre-MCs). All CSF samples were simultaneously analyzed for Aβ42, T-tau and P-tau_{181p} at Sahlgrenska University Hospital, Mölndal, Sweden, using the methods as described previously in detail (Blennow et al., 1995; Vanmechelen et al., 2000; Zetterberg et al., 2008) (**Table 3**).

Table 3. Demographics.

	pre-MC (*n* = 7)	MC (*n* = 10)	NC (*n* = 20)
Age (y)	42.7±8.4	46.5±9.3	48.4±15.1
Gender, M/F	6/1	8/2	11/9
Education, years	12.6±2.1	11.9±2.1	11.4±2.3
MMSE score	29.6±0.5	27.3±5.8	29.2±0.9[a]
APOE ε4 carrier, *n* (%)	4 (57.1)	6 (60.0)	5 (25.0)
Years to AAO (y)	-10.5±9.0	-6.9±9.5	-4.4±12.7
Aβ42, pg/mL	1094.8±666.5[a]	901.1±581.8[a]	1730.1±424.7[b]
P-tau$_{181p}$, pg/mL	45.8±23.3[a]	60.6±30.4[a]	43.2±14.0[b]
T-tau, pg/mL	326.6±183.7[a]	504.1±364.2[a]	297.2±126.0[b]

[a] Data missing for two subjects
[b] Data missing for seven subjects.

T_1-w and DTI were acquired from all the subjects. DTI acquisition parameters are as follows: TR/TE = 8000/97 ms, 60 axial slices, voxel size = 2×2×2.4 mm^3, 30 orientations for the diffusion-sensitizing gradients with b-value of 1000 s/mm^2.

After the same pre-processing as in study II, GM intensity, FA and MD maps were entered into a voxel-wise statistical analysis to compare the difference between pre-MCs/MCs and NCs, adjusted for age, gender, years of education, *APOE* ε4 status (positive or negative) and 'years to AAO'. Similar to study II, the partial correlations between CSF biomarkers and MD values were tested for the whole sample (adjusted for age, gender, years of education and *APOE* ε4 status).

3.6 Paper IV

Twenty-five RRMS patients (6 men, 19 women; age range 30-63 years) were included. Median EDSS score was 1.5 (range=1–6.5) and mean disease duration was 8.5 years (range= 0.3–21.6 years).

The mGRE data for mapping the T_2^* decay curves was acquired with an in-house developed pulse sequence by scientists at the National Institutes of Health (van Gelderen et al., 2012). Thirty-eight echoes (positive read gradient only) were acquired with an echo spacing of 1.6 ms (range from 2.3 to 62.7 ms). TR was 1 s and flip angle 70°. Fifteen slices with 1.5 mm slice thickness with an in-plane resolution of 1.5 mm × 1.5 mm were measured per scan. The slices were parallel to the plane of the anterior and posterior commissure line and captured a section of the corpus callosum.

All mGRE imaging analyses were similar to our previous study (Sati et al., 2013). The average complex signal of interested regions was calculated and fitted to a three-component model using the following equation.

$$S = (A_1 e^{(-1/T^*_{2,1} + i2\pi\Delta f_1)t} + A_2 e^{(-1/T^*_{2,2} + i2\pi\Delta f_2)t} + A_3 e^{(-1/T^*_{2,3})t}) e^{i(2\pi f_g t + \varphi)}$$

Here, A_n is the amplitude, $T^*_{2,n}$ the relaxation time, Δf_n the frequency shift of component *n*, which is defined relative to global / interstitial water frequency f_g, φ is the phase offset. Components 1, 2 and 3 were assigned to myelin, axonal and interstitial water respectively (van Gelderen et al., 2012; Sati et al., 2013). Based on our preliminary data, the starting values for the fitting were defined as $A_1 = 0.16$, $A_2 = 0.43$, $A_3 = 0.41$; $T^*_{2,1} = 6.3\, ms$, $T^*_{2,2} = 41.7\, ms$, $T^*_{2,3} = 26.3\, ms$; $\Delta f_1 = 21\, Hz, \Delta f_2 = -6\, Hz, f_g = 0\, Hz, \varphi = 0\, Hz$. For the analyses of lesions, the $T^*_{2,1}$ and Δf_1 were fixed at values from contralateral NAWM as the myelin water signal in lesions proved to be too small to determine these independently. A range of values was tested, which did not change the results significantly.

A t-test was used to compare differences between enhancing lesions and NAWM, non-enhancing lesions and NAWM, and enhancing versus non-enhancing lesions for the three-component fitting results.

4 RESULTS AND DISCUSSIONS

4.1 Association between functional and structural brain changes and CSF biomarkers in sporadic AD

The time course and spatial distribution of amyloid and tau deposition suggest that the progression of AD shows some regional specificity (Braak and Braak, 1997). Some regions of the DMN showed high levels of amyloid deposition in these patients. Furthermore, the functional connectivity between brain regions of the DMN is disrupted in elderly normal adults with amyloid deposition (Hedden et al., 2009; Sheline et al., 2010). rs-fMRI is thought to be a synaptic biomarker. There is evidence that soluble oligomers of Aβ can selectively impair synaptic plasticity to disrupt synaptic function both in mice model and in vitro (Arendt, 2009). These suggest that this neural activity within DMN may provide information of regional changes caused by amyloid deposition.

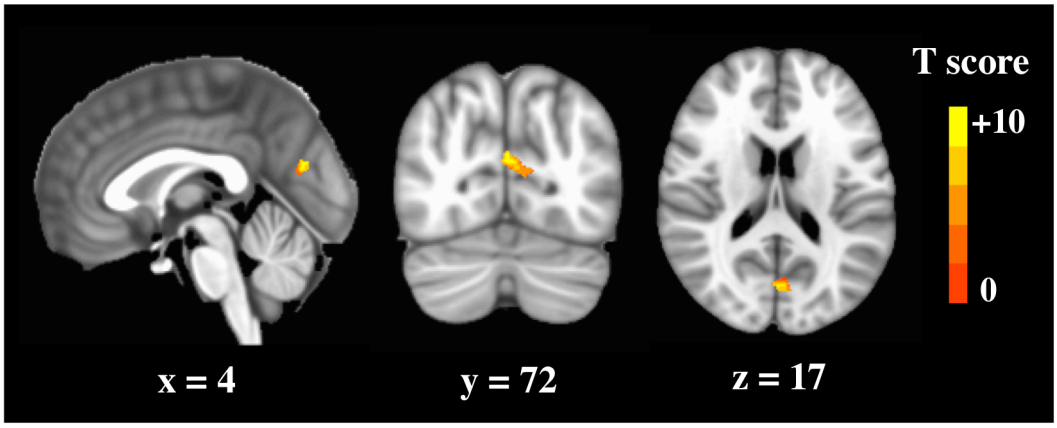

Figure 4. The correlation between functional connectivity within DMN and CSF ratio of Aβ42/P-tau$_{181p}$ in AD. One cluster within DMN shows positive correlation with the ratio of Aβ42/P-tau$_{181p}$, adjusted for age, gender and GM intensity map. The cluster consists of 17 voxels, peak T score is 3.44 and located in left precuneus. However, the most part of the cluster is in the left cuneus.

Low CSF Aβ42 and high T-tau and P-tau$_{181p}$ levels were associated with AD pathology, amyloid plaques and hyperphosphorylated tau, respectively (Seppälä et al., 2012). CSF ratio of Aβ42/P-tau$_{181p}$ showed superior diagnostic usefulness than either measure alone (Maddalena et al., 2003; Ibach et al., 2006). In study I, the correlation of brain functional connectivity within DMN and CSF ratio Aβ42/P-tau$_{181p}$ was investigated. We found a positive correlation between the ratio of Aβ42/P-tau$_{181p}$ and functional connectivity within the DMN in left precuneus/cuneus (**Figure 4**). Anatomical and connectivity data seem to suggest a relevant role for the precuneus in

the implementation of a wide range of cognitive functions, including episodic memory retrieval, visuospatial imagery, self-processing and others (Cavanna and Trimble, 2006). Evidence indicated that precuneuc/cuneus participate during the switching of attention (Le et al., 1998). In addition, the precuneus/cuneus have been reported to be associated with brain changes in AD and MCI patients, such as Aβ42 deposition, cerebral blood flow and glucose metabolism changes (Buckner et al., 2005; Bai et al., 2008; Petrie et al., 2009; Tosun et al., 2011; Luo et al., 2012). Our results are consistent with previous reports. Moreover, the findings support the view that impaired synaptic function, which is evaluated by rs-fMRI is related to amyloid deposition, pathological tau process and progresses with disease severity.

Buckner et al. (Buckner et al., 2005) noted that neuropathology, atrophy, and metabolism all display similar profiles on the cortical surface in patients with AD. After the association between functional changes and CSF biomarkers was observed in study I, the relationships of CSF biomarkers and structural brain changes were investigated in study II. The accumulation of intraneuronal NFTs and extracellular APs are the neuropathologic characteristic of the AD brain, which could lead to neuronal death and disturbances of tissue homogeneity (Chua et al., 2008), and increase water diffusion of brain tissue (Fellgiebel et al., 2004). These structural brain alterations could be indicated by GM volume, FA and MD changes. We found that GM volume and MD changes correlated with CSF Aβ42 and T-tau, FA associated with CSF Aβ42 (**Figure 5**). No significant correlations between P-tau_{181p} and GM volume, FA and MD changes were found; this may be due to the presence of other tau proteins, such as phosphorylated tau at position threonine 231 and serine 199, which have been reported with similar diagnostic performances for AD (Hampel et al., 2004).

It is interesting that the majority of regions with significant correlations between structural brain changes and CSF biomarkers overlapped the DMN and extended to the adjacent WM. It has been demonstrated that the DMN reflects the underlying structural connectivity architecture of the human brain, including the cingulum tract, superior frontal-occipital fasciculus and the genu of the corpus callosum (van den Heuvel et al., 2009; Greicius et al., 2009; Teipel et al., 2010). The regions with significant correlations overlapped the limbic system as well. The limbic system is a group of interconnected cortical and subcortical structures dedicated to linking

emotion to cognition and behavior (Yu et al., 2014). The limbic system plays a key role in AD, which is related to the accumulation of APs and NFTs (Braak and Braak, 1991). Although the exact cause of these changes has not been identified, all our results support the view that AD brain pathological changes, which are reflected by CSF biomarkers, could be detected with rs-fMRI, VBM analysis and DTI measurements.

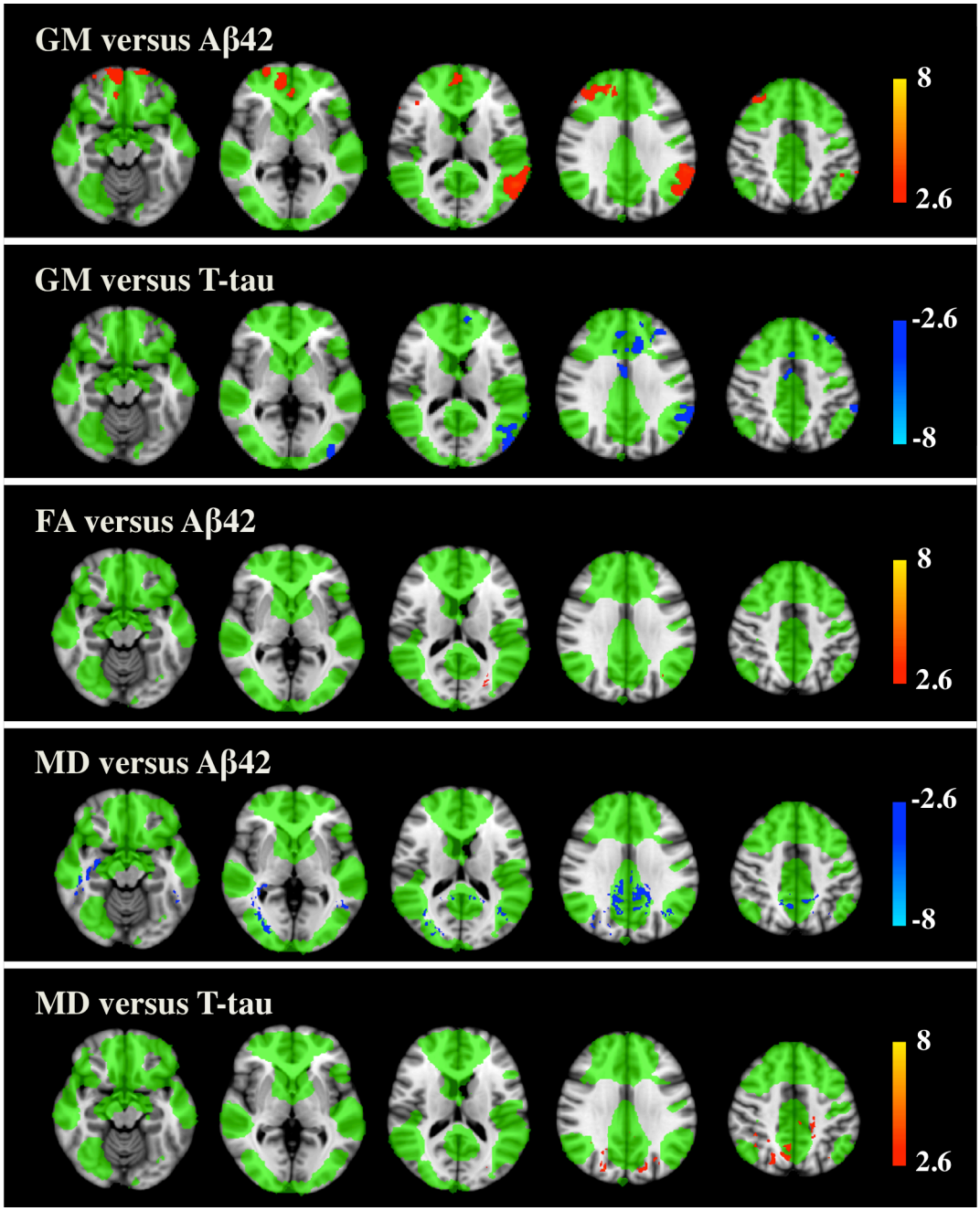

Figure 5. Brain regions with significant correlations between CSF biomarkers and GM volume, FA and MD. The images are overlaid on the MNI template. The green color shows the DMN template. The red and blue colors denote the regions with significant correlations (with cluster-forming threshold $t > 2.66$).

To test whether different MRI modalities could be used effectively to detect AD pathological changes at different disease stages; the relationship between CSF biomarkers and functional connectivity, GM volume, FA and MD changes for each individual diagnostic group was evaluated separately (**Table 4**). In the AD group, only correlation between FA and CSF Aβ42 was observed. In addition, FA was associated with CSF Aβ42 only in occipital cortex and underlying white matter for the entire cohort, which is likely involved in amyloid deposition at the late stage of AD (Braak and Braak, 1991). For the patients with MCI, both rs-fMRI and DTI measurements were associated with CSF biomarkers. While for the subjects with SCI, only MD significantly correlated CSF Aβ42 and T-tau. Taken together, our results support Sperling's hypothetical model of dynamic biomarkers of AD (Sperling et al., 2011), which was adapted from a theory proposed by Jack et al (Jack et al., 2010). None of the biomarkers is static; rates of change in each biomarker change over time and represent a sigmoid shaped trajectory. At a given point in time, rate of change of biomarkers might be different although they have the same shape over the course of disease progression. For the entire cohort, the CSF biomarkers were associated with functional and structural brain changes, whereas the relationship changed at different disease stages. In addition, the biomarker of Aβ deposition, which becomes abnormal early in this model, was associated with MD changes. This suggests that microstructural alterations in the brain indexed by MD are an early event in AD pathogenesis, which could be used to detect pathological changes at an early stage.

Table 4. Partial correlations between CSF biomarkers and rs-fMRI measurement, GM volume, mean FA and MD of the brain regions with statistical significance.

	Total [a]		AD		MCI		SCI	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
rs-fMRI								
Aβ42/P-tau$_{181p}$ [b]	0.33	**< 0.01**	0.03	0.90	0.50	**< 0.01**	-0.08	0.72
GM								
Aβ42 [c]	0.35	**< 0.01**	-0.08	0.75	0.29	0.11	-0.09	0.72
T-tau [c]	-0.30	**< 0.01**	0.21	0.41	-0.15	0.41	-0.06	0.82
FA								
Aβ42 [b]	0.52	**< 0.01**	0.50	**0.03**	0.41	**0.02**	0.40	0.08
MD								
Aβ42 [b]	-0.62	**< 0.01**	-0.39	0.10	-0.60	**< 0.01**	-0.68	**< 0.01**
T-tau [b]	0.65	**< 0.01**	0.36	0.14	0.61	**< 0.01**	0.67	**< 0.01**

[a] Total refers to all subjects with AD, MCI and SCI.
[b] Adjusted for age, gender.
[c] Adjusted for age and gender and intracranial volume.

4.2 Correlation of preclinical structural brain changes and CSF biomarkers in familial AD

The pathophysiological process of AD is thought to begin many years before the diagnosis of AD dementia (Sperling et al., 2011). The increasing age of the population is leading to an increased prevalence of AD in the world. It is critical to identify individuals developing AD at a very early stage and estimate the timing of dementia onset. Studies on familial AD MCs can be particularly valuable for investigating disease progression at early stages due to the high likelihood of developing AD. For this purpose, a small cohort of FAD MCs was studied in study III. We found that MCs showed lower CSF Aβ42 and higher P-tau$_{181p}$ and T-tau levels in the CSF, even though most of them are pre-MCs, which is consistent with previous reports. It also supports the view that AD pathological changes begin many years before onset of clinical symptom.

In our sporadic AD study, correlations between MD changes and CSF Aβ42 and T-tau were observed in SCI group. To further confirm these findings, we compared the

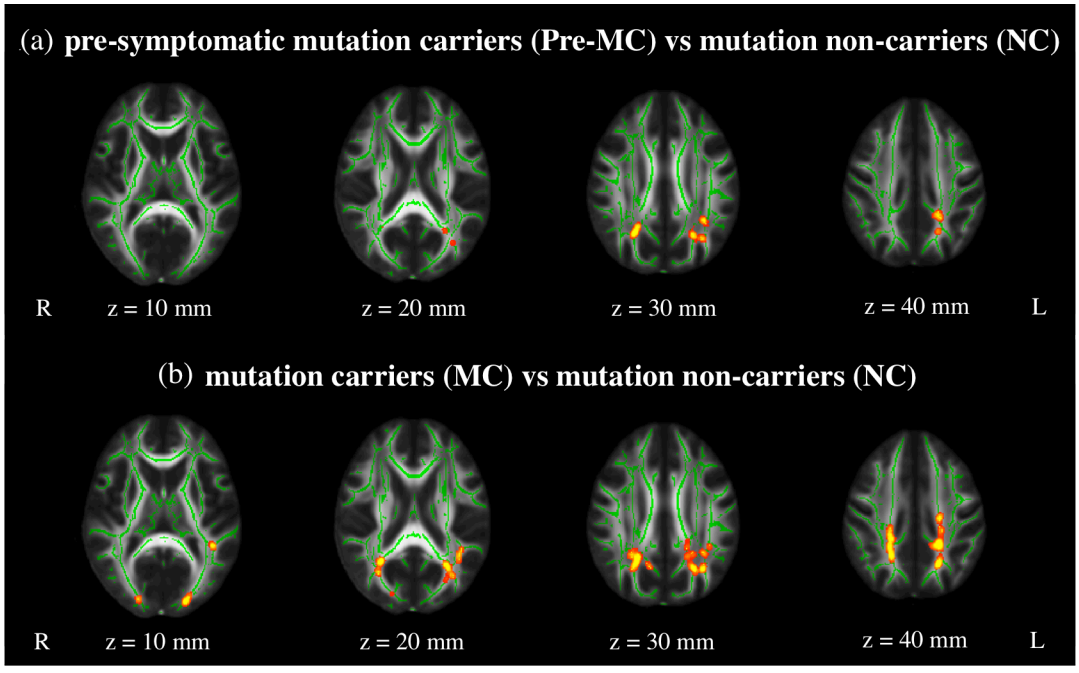

Figure 6. Increased MD in pre-MCs and MCs compared with NCs. (a) MD was significantly increased in the left inferior longitudinal fasciculus and cingulum and bilateral superior longitudinal fasciculus in pre-MCs compared with NCs (red-yellow). (b) When three symptomatic MCs are included in the analysis, the area with significant differences widens (red-yellow).

GM volume, FA and MD between FAD pre-MCs/MCs and NCs in study III. A significantly increased MD in pre-MC compared with NC in the left inferior longitudinal fasciculus and cingulum and bilaterally in the superior longitudinal fasciculus was found (**Figure 6a**). When including the three symptomatic MCs, the regions became wider (**Figure 6b**). There were no significant differences in whole-brain GM volume and FA between pre-MCs and NCs or between MCs and NCs. Interestingly, the regions with statistical significance also overlapped the limbic area. Using the same non-image partial correlation analyses as study I and II, not surprisingly, the mean MD values from these regions showed a statistically significant negative correlation with CSF Aβ42, and positive correlation with P-tau$_{181p}$ and T-tau for all subjects (**Figure 7**). These are all consistent with our previous results that MD may reflect pathology at very early stage and could be a potential biomarker of preclinical AD.

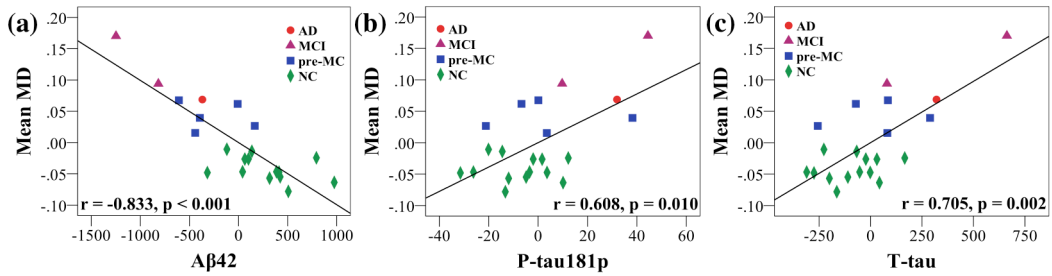

Figure 7. Partial correlations between AD CSF biomarkers and MD. Scatter plots show the partial correlations between CSF Aβ42 (a), P-tau$_{181p}$ (b) and T-tau (c) and MD from regions with a statistically significant difference between the MC and NC groups, adjusted for age, gender, years of education and *APOE* ε4 status. There was a significant negative correlation between the MD value and CSF Aβ42; positive correlations were seen between the MD value and CSF levels of both P-tau$_{181p}$ and T-tau.

4.3 Quantitative analyses of white matter changes in MS lesions

In study IV, a novel MRI technique, involving the fitting of a three-component model to the T_2^* relaxation behavior, was used to detect and characterize ongoing demyelination in MS lesions.

This method provides a measure of the amount of water trapped between the myelin layers, which is generally considered to reflect brain myelin content. The myelin bilayer is made up of lipid and protein. Water fills between the bilayers, which makes up approximately 40% of the weight of myelin (Laule et al., 2007). A decreased amount of myelin water was found in both enhancing and non-enhancing lesions

compared to the contralateral NAWM, which suggests ongoing demyelination in these lesions (**Figure 8a**). Increased interstitial and axonal water indicates water moving from between myelin layers to the extracellular and/or axonal compartments during the demyelination process.

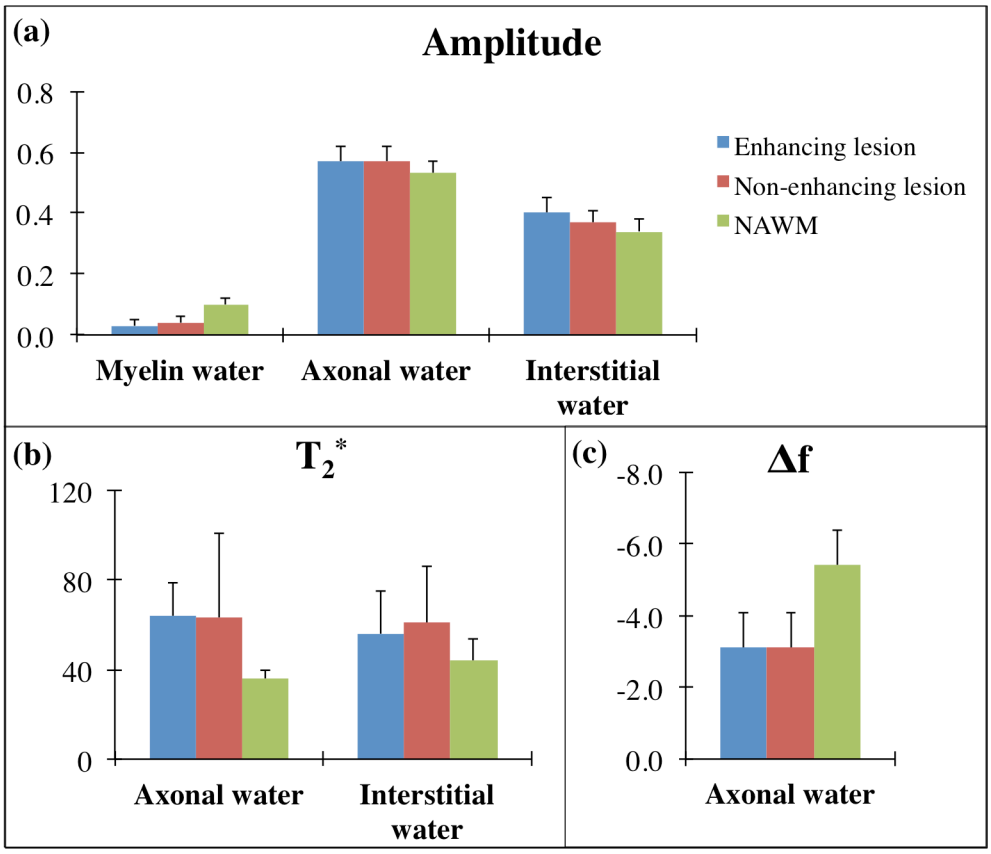

Figure 8. Significance of the differences in three-component fitting results between enhancing and non-enhancing lesions, and NAWM. In both enhancing and non-enhancing lesions, the amplitude of myelin water was significantly decreased, and interstitial and axonal water was increased compare to the contralateral NAWM (a). While comparing with NAWM, lesions also showed longer T_2^* for interstitial and axonal water (b), and lower frequency shift for axonal water (c).

We also found longer relaxation time T_2^* of interstitial and axonal water in lesions when compared to the contralateral NAWM (**Figure 8b**), which has been reported to correspond to the myelin loss in MS lesions (Yao et al., 2012; Lee et al., 2012). In previous T_2-based myelin water studies, the T_2 of myelin water (10ms < T_2 < 50ms) was not well defined, which could lead to a possible overestimation of the myelin water fraction (Du et al., 2007). Moreover, the intra- and extra-cellular water (T_2 ≈ 80-100ms) was computing as one component (MacKay et al., 1994; Laule et al., 2004; Björk et al., 2015). This compartment-specific T_2^* relaxation used in the study arises from differences in water mobility in the different pools, which improved the

accuracy in separation of the three components.

In addition, a smaller frequency shift for axonal water in lesions was observed relative to NAWM (**Figure 8c**). In WM, compartment-specific resonance frequency shifts may occur due to the magnetic susceptibility effects of the distribution of myelin-associated lipids and iron. MRI susceptibility effects in WM have strong contributions from tissue nanostructure and microstructure (Sati et al., 2013). It has been reported that altered frequency contrast indicated myelin damage, which is consistent with our results (Yablonskiy et al., 2012).

These findings suggest that the fitting of a three-component model to the T_2^* decay curve in MS lesions may help to quantify myelin loss. Moreover, in MS lesions, increased T_2^* and lower frequency shift for axonal water could help us further understand the microstructural changes, which may relate to axonal loss and neurodegenerative process.

5 CONCLUSIONS AND FUTURE PERSPECTIVES

In this thesis, we studied functional and structural brain changes in two neurodegenerative diseases, AD and MS, with novel MRI techniques, including rs-fMRI, VBM analysis, DTI and separation of T_2^* relaxation components.

AD is the most common neurodegenerative disease. The disease is currently diagnosed when affected patients meet criteria for dementia, a stage at which the brain has suffered sufficient damage to severely impact cognition. There is increasing recognition that such a late diagnosis poses major challenges for managing the disease and finding effective therapies. Recognizing AD when persons experience only very mild cognitive deficits or subjective cognitive symptoms would support the development of disease-modifying therapies, the identification of a more appropriate therapeutic window, and the determination of individuals who would benefit most from early interventions. In this thesis, rs-fMRI, VBM analysis, DTI were used to investigate brain pathological evolution of AD in a continuum cohort, including AD, MCI, SCI and FAD pre-MCs. We found that functional and structural brain changes detected by MRI, both in sporadic and familial AD, were associated with CSF biomarkers, which are thought to reflect pathological changes in the brain. And these regions with significant changes are relevant to the DMN. We believe that these results will contribute to the understanding of the progression of AD pathology and aid in the diagnosis of AD at an early stage. Moreover, MD is a potential biomarker of preclinical AD.

MS is another common neurodegenerative disease. The clinical courses of MS are heterogeneous with infinite variety of symptoms and unpredictable recurrent attacks (Lucchinetti et al., 2001). The mechanisms of ongoing deterioration observed in progressive MS are still unclear. MS subtypes can be categorized as relapsing or progressive based on the natural history of the disease, but these categories do not provide temporal information about the ongoing disease process. Evidence of disease activity and clinical progression may impact prognosis and therapeutic decisions. Various in vivo MRI techniques have been used to study the pathological evolution of MS. Here, we used a new MRI technique, involving separation of T_2^* relaxation components, to study the demyelination in a clinical MS cohort at 7T. This further validates the feasibility of this new technique to detect demyelination in MS patients

and myelin water fraction as a marker for myelin. It also supports the use of myelin water imaging to study myelin pathology. Moreover, compared to T_2-based myelin water imaging, it improved the accuracy in separation of myelin water, axonal water and interstitial water components due to the compartment-specific T_2^* relaxation and frequency shifts. Furthermore, increased T_2^* and lower frequency shift for axonal water may reflect microstructural changes, probably the axonal damage in MS lesion, and help to further characterize tissue damage in this disease. Additional longitudinal work is warranted, which can lead to a better understanding of, and prognostic ability for, this complex disease.

The experimental findings reported here are consistent with expectations based on prior radiological and pathological work, and are helpful in further understanding pathological evolution in AD and MS. In addition, more and more evidence shows AD, MS and some other neurodegenerative diseases have common features, including pathology. With these novel MRI techniques it is possible to screen individuals susceptible to and/or manifesting functional and structural brain changes with disease pathological evolution. For instance, white matter alterations in confirmed AD are a combination of axonal and myelin alteration (Englund et al., 1988; Bendlin et al., 2012). Histological studies have demonstrated a widespread decrease in myelin that has been observed in normal-appearing white matter, as well as more severe myelin loss in focal regions in AD (Fernando et al., 2004). Biochemical analyses of AD white matter revealed increased quantities of Aβ40 and Aβ42 accompanied by significant decreases in the amounts of myelin protein (Bartzokis, 2004). On the other hand, the finding of APP expression in axons around the plaque in MS, as well as the correlation of Aβ with different stages of MS has clearly indicated that amyloid plays some kind of key role in MS disease pathogenesis (Chandra, 2015). Axonal loss occurs in all demyelinated MS lesions and is considered the main cause of irreversible chronic disease progression in MS (Bitsch et al., 2000). There is increasing evidence that damage to WM can occur either to the myelin or to the axon with subsequent damage to the other (Tsunoda and Fujinami, 2002). The application of the separation of T_2^* relaxation components in AD may help to further understand WM changes in this disease and the underlying mechanisms. Comparison of the relationship between brain changes and amyloid deposition in different

neurodegenerative diseases could be beneficial in understanding disease progression, and in enabling preventive and more effective treatment of the patients.

To conclude, the results presented in this thesis show the potential of novel MRI techniques in detecting pathological evolution of neurodegenerative diseases. These non-invasive techniques may someday be used in clinical practice to help diagnosis and monitor neurodegenerative disease progression. Furthermore, these methods could be used in clinical trials to assist in the development of new drugs.

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