Cognitive Impairment and Autobiographical Memory in Elderly Patients with Multiple Sclerosis - Subtype Classification and Comparison with Alzheimer's Disease

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Meinen Kindern

Tim,

Jakob und Tobias

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Summary

Multiple sclerosis (MS) is one of the most common neurological diseases of the early and middle adulthood and is characterized by inflammatory demyelination and axonal injury in the brain and spinal cord. Whereas inflammatory demyelination traditionally has been seen as the main disease process in MS, axonal damage or loss is receiving increasing attention. In MS brain atrophy affects extensively the white matter and cortical and deep grey matter structures and is closely related to the presence and severity of cognitive impairment. Since neuropsychological examination of elderly patients with MS is not a main focus of current research there are many unresolved questions regarding magnitude and pattern of deficits in this disease. Particularly controversies exist whether deficits are indicative of clinical course and subtype classification. Moreover, Alzheimer's disease-related pathology cannot be ruled out in elderly MS patients as advancing age is the most significant risk factor for developing Alzheimer dementia (AD). Both patients with amnestic mild cognitive impairment (aMCI) or dementia due to Alzheimer's disease and MS show axonal loss and neurodegeneration in cortical areas that are involved in cognitive processing. Similar to Alzheimer's disease these neuropathological changes worsen over time and seem to increase cognitive deterioration in long-term patients with progressive MS subtypes.

The presented work aimed to distinguish MS-related cognitive impairment from Alzheimer's disease-related deficits and to characterize disease-dependent deterioration patterns by comparing age-, education-, and gender-matched groups of elderly patients with relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), aMCI, or early AD using the Autobiographical Memory Interview (AMI) and

the German version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery.

We found substantial episodic memory deficits in the long-term course of SPMS that were associated with deterioration of executive function, but not impairment of memory storage as recognition was preserved in SPMS in contrast to the patients with aMCI.

Furthermore, patients with SPMS, AD, and aMCI, but not with RRMS, exhibited a pattern of episodic autobiographical memory impairment that followed Ribot's Law; older memories were better preserved than more recent memories. In contrast to aMCI and AD, neither SPMS nor RRMS were associated with semantic autobiographical memory impairment.

In summary, our neuropsychological results point at distinct disease mechanisms in different MS subtypes and differentiate between MS-related cognitive impairment and AD-related deficits. Neuropsychological testing may contribute to identify AD-related pathology in SPMS patients since MS-related episodic memory impairment due to deteriorated executive function can be distinguished from AD-related encoding and storage deficits. Moreover, possibly due to neurodegenerative processes in functional relevant brain regions deficits in episodic autobiographical memory are affected in long-term patients with SPMS similarly to that seen in patients with AD or aMCI.

Our results provide baseline data for future investigations to evaluate similarities and differences in the pathophysiology of MS and Alzheimer’s disease, which can be related to the quality and quantity of neuropsychological deficits. It may contribute to generate hypotheses of possible correlations between clinical,

biochemical and imaging markers aiming at a better understanding of the underlying disease mechanisms of MS and Alzheimer. This approach possibly could lead to new diagnostic opportunities since the pathogenic significance of specific biomarkers of MS and Alzheimer's disease is currently poorly understood.

Zusammenfassung

Die Multiple Sklerose (MS) ist eine der häufigsten neurologischen Erkrankungen des frühen und mittleren Erwachsenenalters und ist gekennzeichnet durch entzündliche Entmarkungsherde im Gehirn und Rückenmark. In den vergangenen Jahren konnten neben entzündlichen Prozessen zunehmend neurodegenerative Veränderungen und axonale Schädigung als Kennzeichen der MS-Pathologie herausgearbeitet werden. Im Krankheitsbild der MS zeigt sich insbesondere ein Verlust von weißer und grauer Substanz in kortikalen Bereichen, der im Zusammenhang mit dem Auftreten und der Schwere kognitiver Funktionseinbußen steht. Da neuropsychologische Untersuchungen bei älteren Patienten mit MS nicht im Fokus der empirischen Forschung stehen, sind in Bezug auf das Ausmaß und die Art der kognitiven Funktionseinbußen noch viele Fragen ungeklärt. Insbesondere ist umstritten, ob die unterschiedlichen klinischen Verläufe der MS zu unterschiedlichen kognitiven Defiziten führen oder diese möglicherweise zur Klassifizierung herangezogen werden können. Letzteres ist insbesondere dadurch von Bedeutung, weil gerade bei älteren MS Patienten die Entwicklung einer Alzheimer Demenz (AD) nicht ausgeschlossen werden kann, da das Alter der größte Risikofaktor für die Entwicklung einer solchen Erkrankung darstellt.

Sowohl Patienten mit einer amnestischen leichten kognitiven Störung (aMCI) als auch Patienten mit AD und MS zeigen axonale Schäden und Neurodegeneration in Hirnregionen, die für höhere kognitive Prozesse von Bedeutung sind. Ähnlich wie bei der Alzheimer Erkrankung nehmen diese neuropathologischen Prozesse im Laufe der Zeit zu und scheinen gerade bei chronischen MS-Verläufen zu einer Zunahme der kognitiven Defizite zu führen.

Die hier vorgestellten Untersuchungen hatten das Ziel, MS-assoziierte kognitive Defizite von denen bei der Alzheimer Erkrankung zu differenzieren und verlaufsformabhängige Defizitmuster aufzuzeigen. Dafür wurde eine alters-, bildungs- und geschlechter-homogene Gruppe älterer Patienten mit schubförmig-remittierender MS (RRMS), sekundär progredienter MS (SPMS), aMCI und beginnender AD neuropsychologisch untersucht. Wir verwendeten dafür das Autobiographische Gedächtnisinterview (AMI) und die deutsche Version der Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Testbatterie.

Bei Patienten mit SPMS zeigten sich erhebliche Defizite im freien Abruf episodischer Gedächtnisinhalte, die mit Defiziten in den Exekutivfunktionen assoziiert waren und nicht auf eine Konsolidierungsstörung hindeuteten, da die Rekognitionsleistung, im Gegensatz zu Patienten mit aMCI, erhalten war.

Des Weiteren zeigte sich bei SPMS, beginnender AD und aMCI, jedoch nicht bei RRMS ein zeitlicher Gradient in der Erinnerungsfähigkeit an autobiographisch-episodische Gedächtnisinhalte - weiter zurückliegende Ereignisse konnten besser abgerufen werden als kürzer zurückliegende Ereignisse. Im Gegensatz jedoch zu den Patienten mit aMCI und beginnender AD zeigten weder Patienten mit SPMS noch RRMS Defizite im Abruf autobiographisch-semantischer Gedächtnisinhalte.

Zusammenfassend weisen unsere neuropsychologischen Ergebnisse auf unterschiedliche Krankheitsmechanismen in den MS-Subtypen hin und ermöglichen außerdem eine krankheitsspezifische Differenzierung der kognitiven Defizite zwischen MS und Alzheimer. Neuropsychologische Testverfahren können daher dazu beitragen, Alzheimer-typische kognitive Veränderungen bei MS Patienten zu erfassen. Gedächtnisdefizite lassen sich bei diesen Patienten auf Einschränkungen

der Exekutivfunktionen zurückführen, die den freien Abruf betreffen, während bei der Alzheimer-Erkrankung sowohl Abruf- als auch Speicherdefizite zu beobachten sind. Außerdem lassen sich bei Patienten mit SPMS Defizite im autobiographisch-episodischen Gedächtnis möglicherweise auf neurodegenerative Prozesse in ähnlichen Hirnarealen zurückführen, wie sie auch bei aMCI und beginnender AD zu beobachten sind.

Unsere Daten stellen eine Grundlage für weitere Untersuchungen dar, in denen Ähnlichkeiten und Unterschiede in der Pathophysiologie von MS und der Alzheimer-Erkrankung in Abhängigkeit von der Qualität und dem Ausmaß neuropsychologischer Defizite verglichen werden können. Aus möglichen Korrelationen zwischen klinischen, biochemischen und bildgebenden Markern können Hypothesen generiert werden, die auf ein besseres Verständnis der zugrundeliegenden Krankheitsmechanismen von MS und Alzheimer zielen. Dies könnte wiederum zu neuen diagnostischen Möglichkeiten führen, da die pathogenetische Wertigkeit bestimmter Biomarker bei MS und der Alzheimer Erkrankung derzeit weitestgehend ungeklärt ist.

1 Introduction

Multiple sclerosis (MS) is one of the most common neurological diseases of the early and middle adulthood. It is characterized by inflammatory demyelination and axonal injury in the brain and spinal cord (Trapp & Nave, 2008). The range of symptoms includes motor, neuropsychiatric, and cognitive dysfunction (Chiaravalloti & DeLuca, 2008).

Alzheimer's disease is a slowly progressive neurodegenerative disorder that typically begins in late life with insidious onset and results in a progressive dementia (Dubois et al., 2007). Cognitive impairment is characterized by deterioration of episodic memory and deficits in word-finding skills, judgment, decision-making, spatial cognition and executive functions (Dubois et al., 2007).

Recent data suggest similarities in certain mechanisms of neurodegeneration between MS and Alzheimer's disease despite their different cause and pathogenesis (Lassmann, 2011). Alzheimer's disease is characterized by pathological changes in the extracellular space and within neurons (Dubois et al., 2010). This process mainly leads to neuronal and synaptic loss that results in functional interruption within the cerebral cortex (Blennow et al., 2006; Dubois et al., 2010). In contrast, MS is primarily a chronic immune-mediated inflammatory disease characterized by demyelination in the white and gray matter (Bjartmar & Trapp, 2001). However, MS shows axonal bisection and neuronal and synaptic loss that is strongly associated with permanent neurological disability and cognitive impairment (Chiaravalloti & DeLuca, 2008; Lassmann, 2011; Stadelmann, 2011; Trapp & Nave, 2008). Despite these different causes and pathogenesis, recent data suggests that

neurodegeneration in MS and Alzheimer's disease share significant pathogenetic mechanisms, which include inflammation, grey and white matter lesions, and mitochondrial dysfunction that subsequently lead to cognitive deterioration in both patients with MS and Alzheimer's disease (Amato et al., 2006; Blennow et al., 2006; Bodling et al., 2009; Chiaravalloti & DeLuca, 2008; Comi et al., 1995; Denney et al., 2004; Denney et al., 2005; Desgranges et al., 2002; Dubois et al., 2010; Dubois et al., 2007).

Up until now few studies have examined cognitive deficits in elderly patients with different forms of MS (Bodling et al., 2009; Smestad et al., 2010). Therefore, many questions regarding their magnitude and pattern remain unresolved. Controversies exist whether deficits are indicative of clinical course and subtype classification. Moreover, as advancing age is the most significant risk factor for developing Alzheimer dementia (AD) (Hampel et al., 2011), Alzheimer's disease-related pathology cannot be ruled out in elderly MS patients. Therefore, it is of great significance to distinguish MS-related cognitive impairment from AD-related deficits. However, it is also important to demonstrate similarities of cognitive deterioration in AD and MS to direct research for shared pathogenic mechanism in the two diseases.

Therefore, the presented neuropsychological studies (Chapter 4 and 5) aimed to characterize disease-dependent deterioration patterns by comparing age-, education-, and gender-matched groups of elderly patients with relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), amnestic mild cognitive impairment (aMCI), or early AD using the Autobiographical Memory Interview (AMI) (Kopelman et al., 1989) and the German version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery (Barth et al., 2005; Morris et al., 1989).

Following a description of epidemiology, pathogenesis, clinical characteristics, diagnosis and neuropsychology of MS (Chapter 2) and Alzheimer's disease (Chapter 3) the first study (Chapter 4) compared autobiographical memory (AM) retrieval in an education- and gender-matched sample of healthy controls (HC) and patients with aMCI, early AD, RRMS, or SPMS, using the AMI (Kopelman et al., 1989). In light of distinct disease mechanisms, we evaluated autobiographical memory in different MS subtypes (i.e. RRMS and SPMS) and hypothesized that SPMS patients would exhibit a graded loss of AM akin to that seen in patients with early AD or aMCI possibly due to neurodegeneration in brain areas that are functionally relevant for AM encoding and retrieval. In contrast, we predicted that patients with RRMS, in which inflammatory activity and demyelination dominate (Kutzelnigg et al., 2005) and primarily affect speed of information processing (Denney et al., 2004), would exhibit normal AM similar to that of HC participants.

In a second study (Chapter 5) we sought to identify disease-dependent deterioration patterns by comparing age-, education-, and gender-matched elderly patients with SPMS and aMCI using the CERAD test battery (Barth et al., 2005; Morris et al., 1989). We hypothesized that aMCI would be characterized by episodic memory loss with learning, retrieval and recognition deficits as this is considered as a reliable (neuropsychological) indicator of prodromal Alzheimer’s disease (Dubois et al., 2007). Deficits in patients with SPMS should be associated with more global cognitive deficits related to inflammation- and atrophy-induced functional disturbances (Ceccarelli et al., 2008; Roosendaal et al., 2011; Sicotte et al., 2008), including reduced attention and processing speed, impaired executive function

(Ceccarelli et al., 2008; Wachowius et al., 2005), and deficits in verbal learning and retrieval, but with sparing of recognition ability (Chiaravalloti & DeLuca, 2008).

Chapter 6 provides a general discussion and a critical reflection of this dissertation, and suggestions for further research.

2 Multiple Sclerosis

2.1 Epidemiology

MS is one of the most common neurological disease occurring between early to middle adulthood. It affects approximately 2.5 million people worldwide and about 500.000 individuals in Western Europe (Pugliatti et al., 2006). In Germany there are about 120.000 patients with MS with incidence rates of 4.6/100.000/year and prevalence rates of 83-127 per 1000 with a female:male ratio of 1.8 (Hein & Hopfenmuller, 2000; Pugliatti et al., 2006) (Figure 1).

Disease onset typically occurs between 2nd and 4th decade (Haussleiter et al., 2009; Noseworthy et al., 2000). However, though it is extremely rare, MS has also been diagnosed before the age of 10 years and even in children as young as 10-months old (Compston & Coles, 2002). Two to five percent of patients experience their first clinical symptom before 16 years of age (Ness et al., 2007; Qiu et al., 2010). Nevertheless, MS can have a late onset (Awad & Stuve, 2010; Leyhe et al., 2005) with an estimated percentage of 9-14% of MS patients aged ≥65 years (Minden et al., 2004). Thus, given an estimated world wide prevalence of 2.5 million physician-diagnosed patients with MS, it is estimated that there are currently 225.000–350.000 people with MS aged ≥ 65 years (Minden et al., 2004).

2.2 Pathogenesis

In 1838 Carswell described the macroscopic neuropathological changes associated with MS (Murray, 2009). Thirty years later these changes were formally

defined as a clinical entity by Charcot (Murray, 2009) who termed it “sclerose en plaques”. Nowadays, MS is seen as a result of a multifaceted interaction between environmental and polygenetic factors (Noseworthy et al., 2000). A number of immunologically relevant genes particularly the human leukocyte antigen (HLA) DR15 haplotype in Caucasians (Nessler & Bruck, 2010) are associated with susceptibility to MS (Giovannoni & Ebers, 2007). This vulnerability becomes meaningful only in the context of environmental factors (Gourraud et al., 2012) including viral infections, such as the Epstein-Barr virus (Ascherio & Munger, 2010), smoking (Ascherio & Munger, 2008; Di Pauli et al., 2008), and vitamin D deficiency (Simon et al., 2012). As risk declines when people migrate away from high prevalence areas geographical patterns in the prevalence of MS are assumed to be contributory agents (Figure 1) (Ascherio & Munger, 2007).

Summarizing, MS seems to be an immune-mediated disorder that occurs in genetically susceptible individuals, with vulnerability being related to some environmental trigger (Noseworthy et al., 2000).

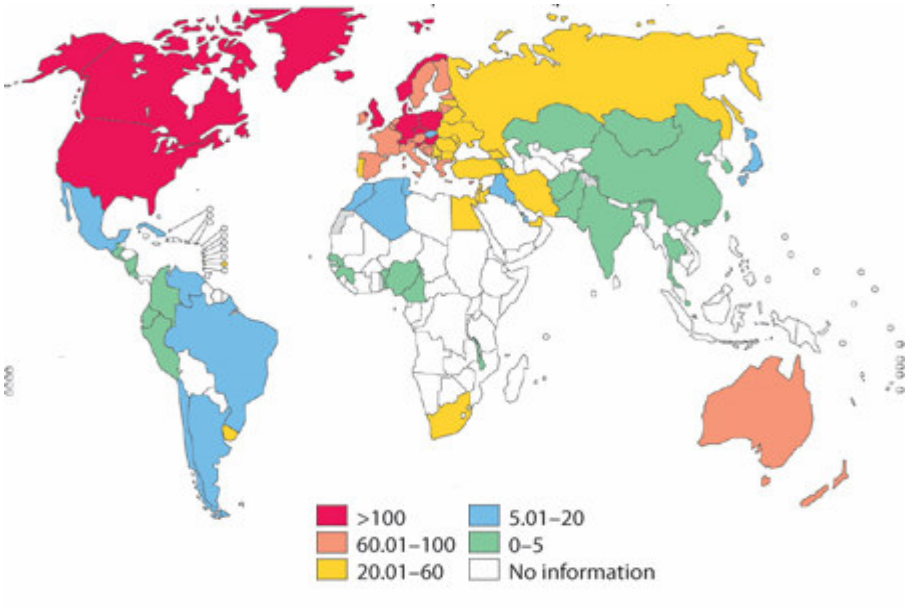

Figure 1. Geographical prevalence of Multiple Sclerosis (MS) per 100.000 population world-wide. MS is more likely to occur in communities in the further Northern and Southern Latitudes. Rates in northern regions can be as much as 5 times greater. If persons migrate from a high-risk to a low-risk region before the age of 15 they take on the lesser risk. This indicates that a genetic susceptibility becomes meaningful only in the context of environmental triggers, and the age of exposure to as yet unknown environmental factors. Adapted from Milo & Kahana (2010)

2.3 Clinical characteristics and diagnosis of Multiple Sclerosis

MS is a chronic demyelinating disease of the central nervous system (CNS) leading to progressive deterioration of neurological functions triggered by inflammatory processes and neurodegenerative mechanisms (Nessler & Bruck, 2010). In the context of MS demyelination involves the inflammatory driven destruction of the myelin sheath around axons in the CNS. The myelin sheath is white in appearance (the white matter of the brain) and increases the speed at which impulses propagate along the axon and the CNS (Figure 2) (Stadelmann, 2011).

There is evidence that secondary to the myelin loss axonal damage occur (Bjartmar & Trapp, 2001). Additionally, plaque formation takes place when glial cells

form fibrous scars after neurodegenerative changes due to demyelination and axonal damage (Stadelmann, 2011; Trapp & Nave, 2008).

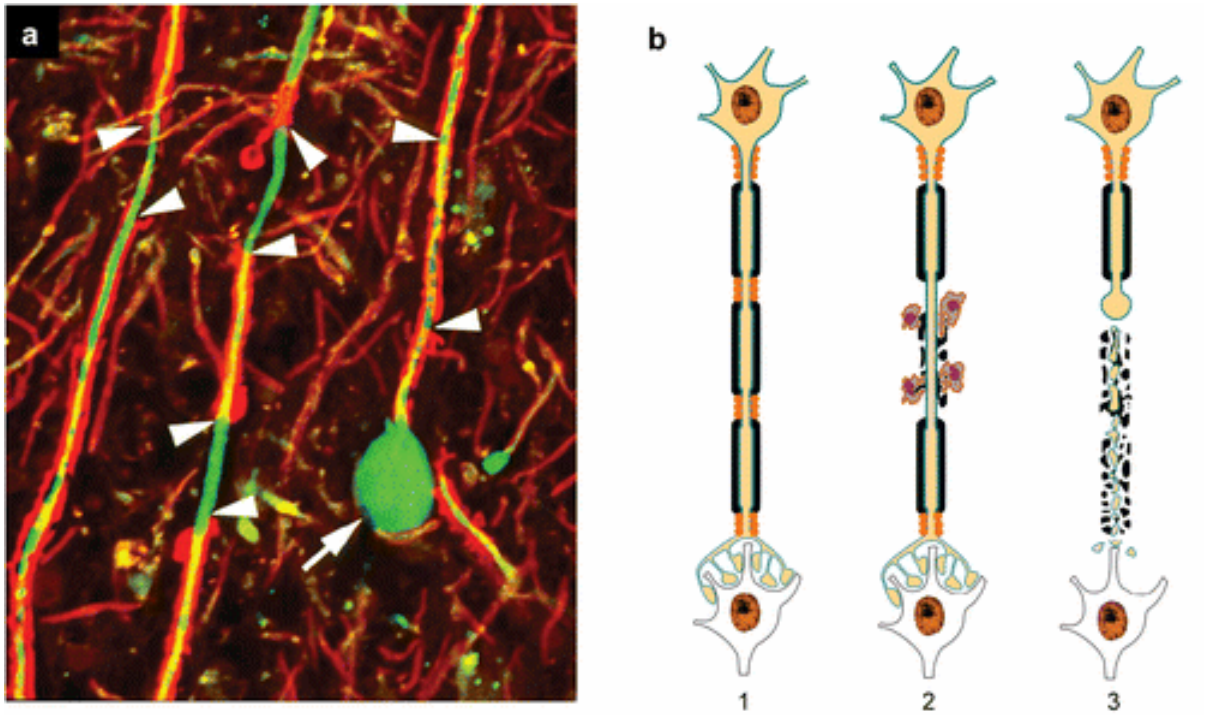

Figure 2. Axons are transected during inflammatory demyelination. (A) Confocal image of an actively demyelinating MS lesion stained for myelin protein (red) and axons (green). The three vertically oriented axons have areas of demyelination (arrowheads), which is mediated by microglia and hematogenous monocytes. The axon on the right ends in a large swelling (arrowhead), or axonal retraction bulb, which is the hallmark of the proximal end of a transected axon. (B) Schematic summary of axonal response during and following transection. 1. Normal appearing myelinated axon. 2. Demyelination is an immune-mediated or immune cell–assisted process. 3. The distal end of the transected axon rapidly degenerates while the proximal end connected to the neuronal cell body survives. Following transection, the neuron continues to transport molecules and organelles down the axon, and they accumulate at the proximal site of the transection. These axon retraction bulbs are transient structures and degenerate. Adapted from Trapp & Nave (2008).

In general, demyelination occurs in white matter surrounding the ventricles of the brain, along the optic nerve, the brain stem, cerebellum and white matter of the spinal cord (Nessler & Bruck, 2010; Noseworthy et al., 2000). More recently, there is evidence that grey matter is also affected by MS (Polman et al., 2011) but the extent depends on MS subtype (Fox & Cohen, 2001; Pagani et al., 2005; Stadelmann et al., 2008) (Figure 3). Demyelination and inflammatory activity seems to be the dominant

process in RRMS (Kutzelnigg et al., 2005) whereas slowly expanding demyelinating lesions and neurodegenerative events predominate in SPMS (Ceccarelli et al., 2008; Kutzelnigg et al., 2005; Roosendaal et al., 2011).

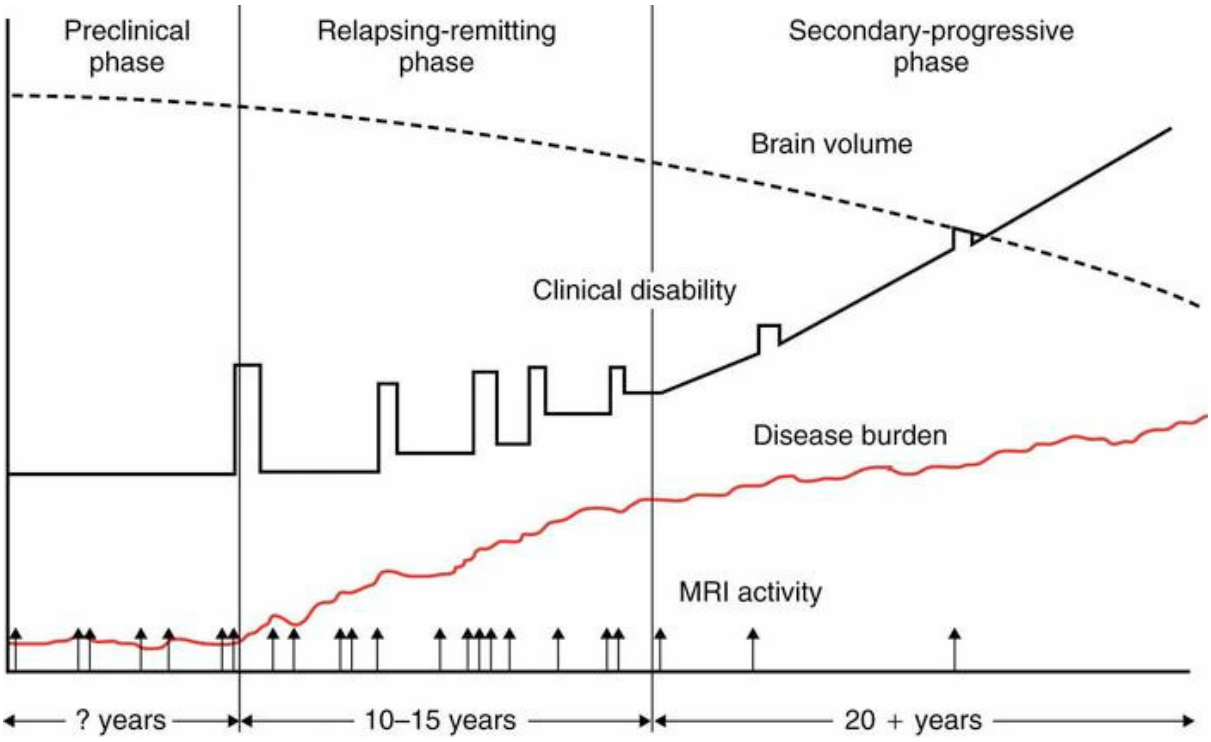

Figure 3. Typical clinical and magnetic resonance imaging (MRI) course of relapsing–remitting and secondary progressive multiple sclerosis. MRI activity (vertical arrows) indicates an inflammatory process as measured on brain MRI. MRI activity typically is more frequent than clinical relapses (spikes in clinical disability), which indicates that more disease activity is taking place than is clinically apparent. Loss of brain volume and increase in disease burden (total volume of lesions), both measured on MRI, indicate permanent tissue damage, which is present early in the disease and gradually progresses over time. Adapted from Fox & Cohen (2001).

MS has a broad variety of clinical expressions, depending on the location and the pattern of neurodegenerative changes and lesions within the nervous system, as well as the type of MS disease course (Chiaravalloti & DeLuca, 2008; Denney et al., 2005; Nylander & Hafler, 2012) (Figure 4).

The most frequent initial symptoms of MS are disorders of sensory function (Calabresi, 2004; Compston & Coles, 2002). Feelings of clusminess or complaints of

dropping things are frequently reported. Other sensory symptoms related to optic neuritis are changes in contrast sensitivity, loss of sight in the central field of vision, blurring of vision, or visual deformation (Cerovski et al., 2005). Disorders of motor function are also common. Furthermore, ataxia, tremor, dysarthria, spasticity and weakness in muscles are commonly experienced (Calabresi, 2004). Fatigue, a syndrome characterized by extremely exhaustion, is also a very widespread symptom of MS, experienced by over half of people during disease course (Bakshi et al., 2000). It is both one of the most commonly reported and seen as one of the worst symptom of MS. The experience of fatigue is mainly seen as a symptom in itself and not as previously assumed caused by depressive symptoms, poor sleeping, or as a side effect of medication (Bakshi et al., 2000). Another cluster of symptoms relates to autonomic dysfunction, and includes aspects of bladder and bowel function as well as orthostatic intolerance, or sexual dysfunction (Haensch & Jorg, 2006).

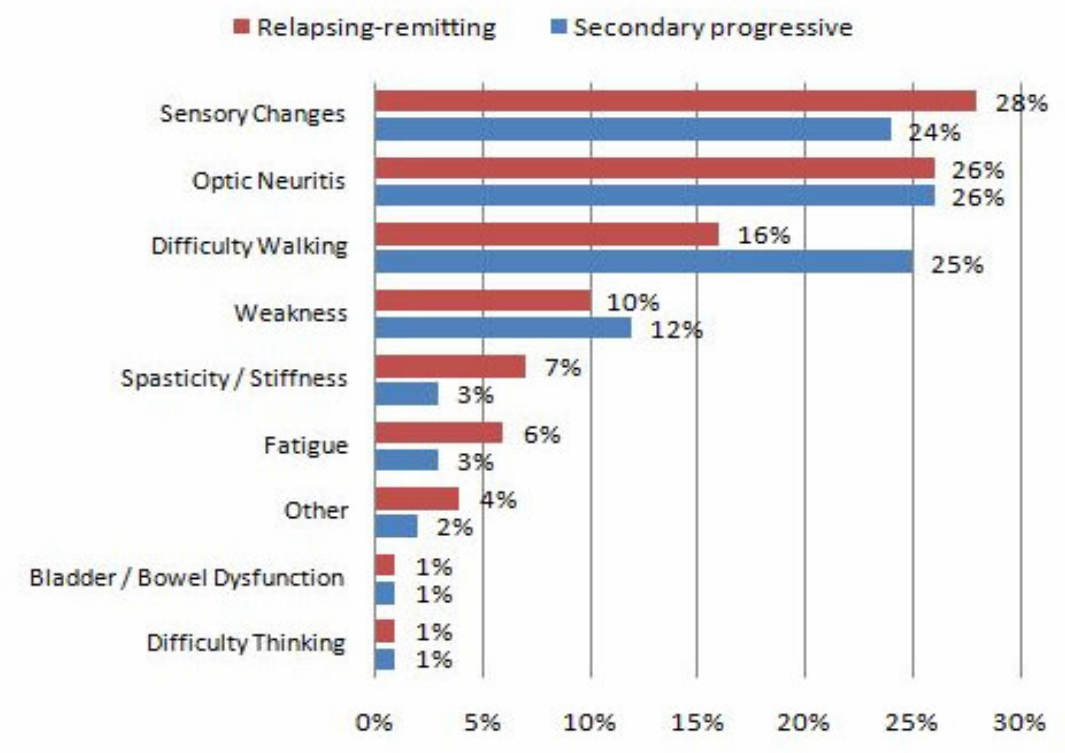

Figure 4. Distribution of initial symptoms for patients with relapsing-remitting and secondary progressive multiple sclerosis. Adapted from Compston & Coles (2002).

According to the McDonald criteria (McDonald et al., 2001) the diagnosis principally based on medical history and physical exam. However, to consider the increased reliance on imaging for lesion dissemination and identification a revision of these criteria was indispensable (Polman et al., 2005; Polman et al., 2011). The new criteria specify that the neurologic lesions should be disseminated in both space and time to distinguish them from acute disseminated encephalomyelitis, a monophasic self-limiting disease, and should reflect a pattern of neurological inflammation typical of MS in the absence of a more appropriate diagnosis (Polman et al., 2005; Polman et al., 2011). A diagnosis of MS reflects clinical evaluation of episodes of alternating neurological impairment and may take into account laboratory data, such as the characteristic oligoclonal bands in the cerebrospinal fluid, which point towards

intrathecal immunoglobulin production, or abnormal visual evoked responses in the absence of optic neuritis (Polman et al., 2011).

The updated criteria (Polman et al., 2011) avoid erroneous attribution of symptoms and signs in young adults to MS thus leading to an earlier and more precise diagnosis before changes in the CNS might interfere with daily self care (Compston & Coles, 2008; McDonald et al., 2001; Polman et al., 2005). When clinical evidence is not sufficient for establish the diagnosis or the diagnosis is indefinite, paraclinical features can be crucial. MRI shows focal or confluent aberrations in white matter in more than 95% of patients (Compston & Coles, 2008). However, as characteristic radiological lesions can also appear in people without clinical disease signs and in many individuals older than 50 years their occurence alone does not substantiate the diagnosis of MS. Therefore, the serially used MRI is indicated as it can show new plaques appearing over time that is a more significant reference for a clinical episode under the new diagnostic criteria (Polman et al., 2011) than an unique MRI scan of the anatomical dissemination (Compston & Coles, 2008) (Figure 5). It must be taken into account that lesions detected in the spinal cord are invariably atypical at any age of an individual. Furthermore, prolonged latency of evoked potentials reflects the specific effect of demyelination on saltatory conduction associated in MS. The presence of oligoclonal bands after protein electrophoresis of the cerebrospinal fluid, which is seen in about 90% of patients, suggests intrathecal immunoglobulin synthesis (Compston & Coles, 2008; Polman et al., 2011).

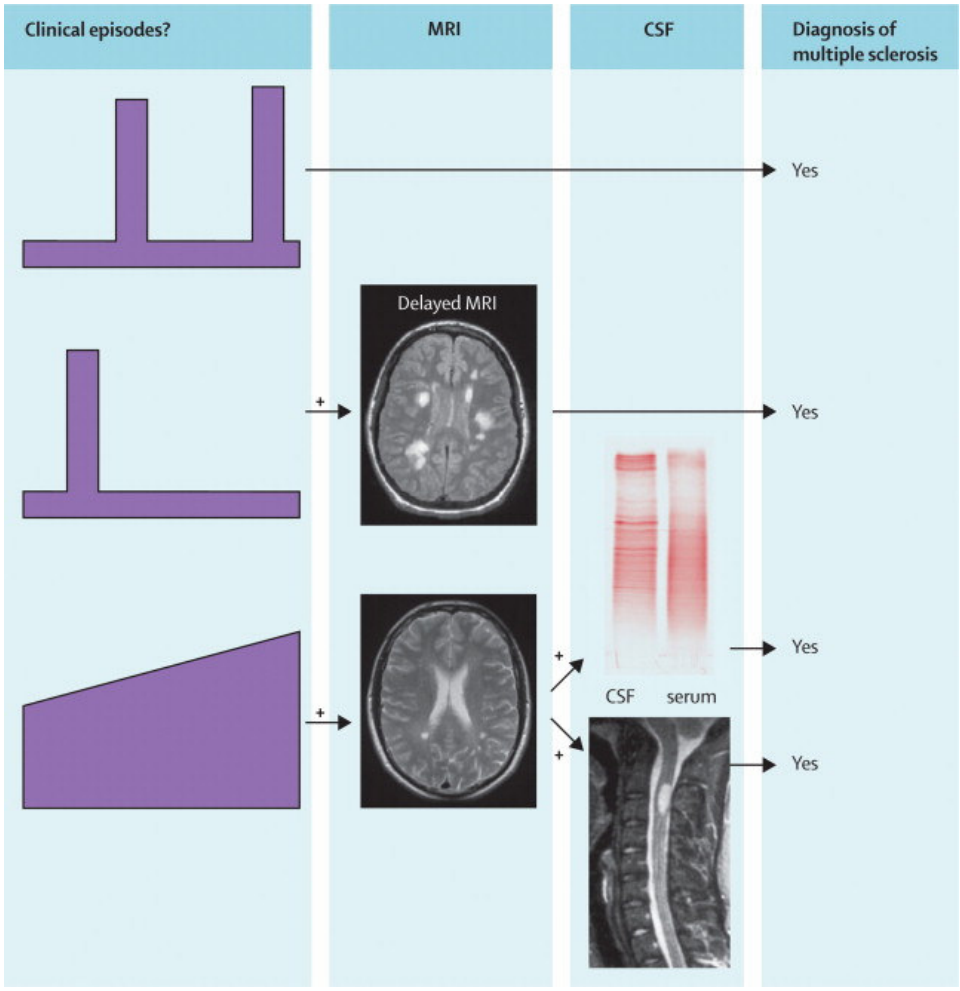

Figure 5. Criteria for the diagnosis of MS. Modified from the McDonald criteria (Polman et al., 2011). The principle is to establish dissemination in time and place of lesions (i.e. episodes affecting separate sites within the CNS have occurred at least 30 days apart). MRI can substitute for one of these clinical episodes. Dissemination in time of magnetic resonance lesions requires: one gadolinium-enhancing lesion at least 3 months after the onset of the clinical event; or a new T2 lesion compared with a reference scan done at least 30 days after onset of the clinical event. In the case of recurrent stereotyped clinical episodes at the same neurological site, criteria for MRI definition of dissemination in space are three features from: (1) one gadolinium-enhancing lesion or nine T2 MRI lesions; (2) one or more infratentorial lesions; (3) one or more juxtacortical lesions; or (4) three or more periventricular lesions; (a spinal cord lesion can replace some of these brain lesions). Primary progressive MS can be diagnosed after 1 year of a progressive deficit and: (1) a positive brain MRI; (2) a positive spinal cord MRI; and (3) positive oligoclonal bands. Patients having an appropriate clinical presentation, but who do not meet all of the diagnostic criteria can be classified as having possible MS. Adapted from Compston & Coles (2008).

The clinical classification of MS patients basically relies on the disease course (Lublin & Reingold, 1996). Each of the three main subtypes has an associated clinical pattern; episodic worsening with remission (RRMS), progressive deterioration

in function (primary progressive MS [PPMS]), or a combination of the two courses (SPMS) (Lublin & Reingold, 1996).

RRMS is the most common form of the disease comprising 75-80% of consecutive MS referrals in some studies (Noseworthy et al., 2000). This disease pattern is characterized by clearly defined acute attacks with full recovery (Figure 6) or with residual deficit upon recovery (Figure 7). Periods between disease relapses are characterized by a lack of disease progression. Approximately 85% of people with MS begin with a relapsing-remitting course. An estimated 65% of RRMS patients will eventually go on to develop the secondary progressive course within a period of 10-25 years (Noseworthy et al., 2000).

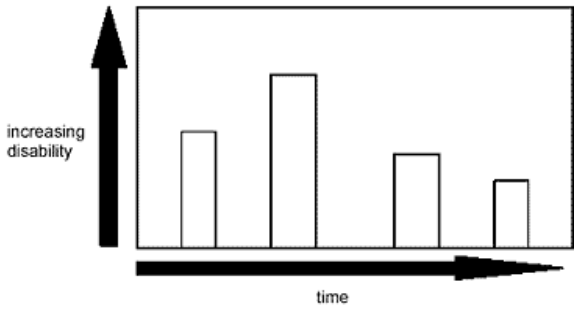

Figure 6. Relapsing-remitting MS disease course characterized by clearly defined acute attacks with full recovery.

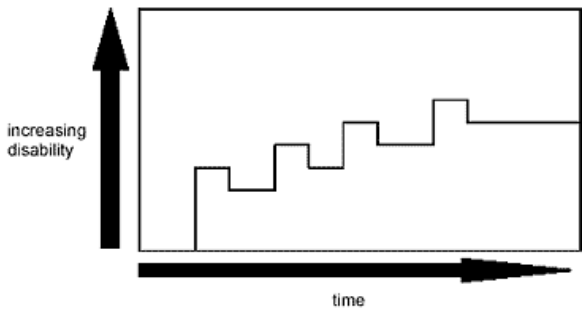

Figure 7. Relapsing-remitting MS disease course characterized by clearly defined acute attacks with residual deficit upon recovery.

SPMS usually begins with an initial relapsing-remitting disease course, followed by increasing disability (Figure 8) that may include sporadic relapses and minor remissions and plateaus (Figure 9). Typically, secondary-progressive MS is characterized by less recovery following attacks, persistently worsening functioning during and between attacks, and/or fewer and fewer attacks accompanied by progressive disability.

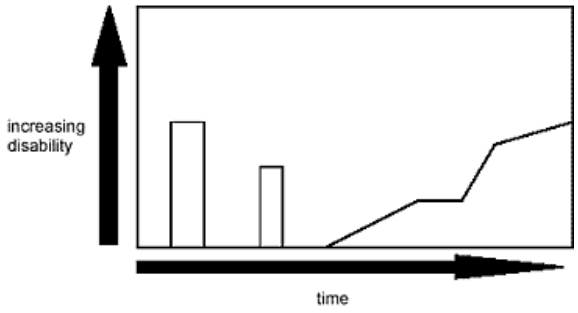

Figure 8. Secondary progressive MS disease course with initial clearly defined acute attacks followed by progression of disability.

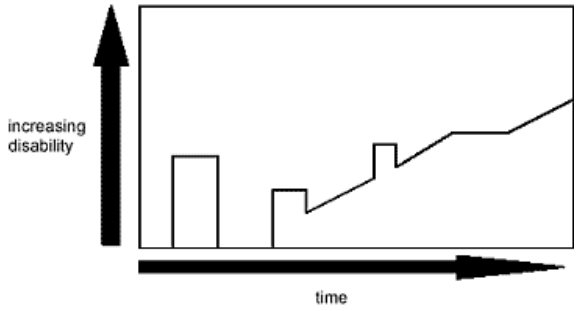

Figure 9. Secondary progressive MS disease course with occasional relapses and minor remissions and plateaus.

A less frequent clinical phenotype, PPMS, encompasses 10% to 15% of the population with MS and is characterized by a progression of disability from onset of disease without plateaus or remissions (Figure 10) or with occasional plateaus and temporary minor improvements (Figure 11). PPMS differs from the other MS

subtypes in a number of ways: men are as likely to develop primary progressive disease as women, disease onset is typically later in life (mid-30s to early 40s), initial disease activity is often in the spinal cord although there is later brain involvement and it is characterized by severe atrophy and axonal degeneration (Bruck et al., 2002; Noseworthy et al., 2000).

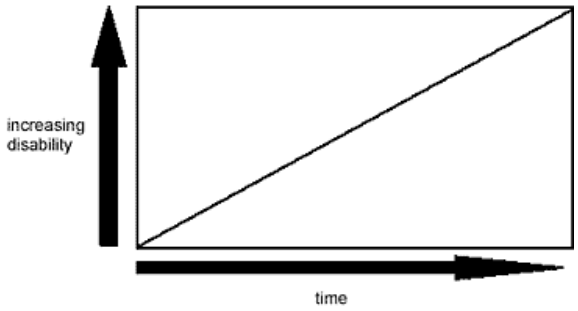

Figure 10. Primary progressive MS disease course with progression of disability from onset of disease without plateaus or remissions.

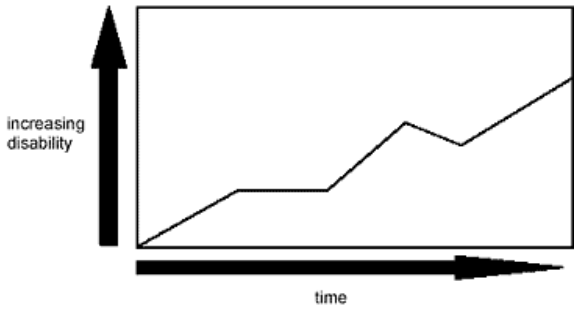

Figure 11. Primary progressive MS disease course with occasional plateaus and temporary minor improvements.

2.4 Neuropsychology

Cognitive impairment is a common symptom of MS that arises in 40-70% of the patients (Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008) irrespective of disease form (relapsing-remitting vs. progressive) (Chiaravalloti & DeLuca, 2008) and at both the earlier (Duque et al., 2008) and later stages of the disease (Bodling et al., 2009; Smestad et al., 2010). Nevertheless, for a long time the prevalence of cognitive deficits in MS has been underestimated (Amato et al., 2006) notably when they are focal rather than global or subtle, particularly in the early phases (Amato et al., 2006; Chiaravalloti & DeLuca, 2008). In such cases cognitive dysfunction might be undetected during brief office visits without performing a formal neuropsychological assessment with standardized test batteries. Additionally, cognitive deterioration in patients with MS is characterized by great inter-patient variability (Amato et al., 2006; Chiaravalloti & DeLuca, 2008).

Considering the high incidence of cognitive deterioration in patients with MS (Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008), sufficient assessment and diagnosis of these deficits is crucial. Disability level measured on the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) is a weak predictor of cognitive dysfunction on most neuropsychological measures (Chiaravalloti & DeLuca, 2008; Rao et al., 1991) as the scale is heavily weighted for motor abilities and therefore relatively insensitive to cognitive changes (Kurtzke, 1983).

There is a variety of neuropsychological tests that may help clinicians and researchers to examine, objectify and quantify cognitive deterioration frequently seen in these patients. As the cognitive deficits in MS often can be subtle and fall within specific cognitive domains or fluctuate considerably among patients (Amato et al.,

2006; Chiaravalloti & DeLuca, 2008), a carefully selected neuropsychological test battery is essential. The minimal assessment of cognitive function in MS (MACFIMS) test battery, the result of an international conference of MS experts, is now recommended for use with patients with MS (Benedict et al., 2006). Similar to the CERAD test battery (Morris et al., 1989) the MACFIMS (Benedict et al., 2006) is composed of seven tests that assess word fluency, visuospatial ability, verbal and visuospatial memory, processing speed, working memory, and executive function, and has been shown to be responsive to the cognitive profiles characteristic of patients with MS (Benedict et al., 2006).

Empirical studies using magnetic resonance imaging (MRI) show distinct correlations with brain lesion burden, brain atrophy, and cognitive deficits (Riccitelli et al., 2011; Rovaris et al., 2006; Zivadinov et al., 2001). Brain atrophy is a well-known feature of MS affecting extensively the white matter and cortical and deep grey matter structures (Amato et al., 2004; Cifelli et al., 2002; Sailer et al., 2003; Zivadinov et al., 2001). It is closely related to the presence and severity of cognitive deterioration in MS patients (Riccitelli et al., 2011; Rovaris et al., 2006; Zivadinov et al., 2001). Overall, these studies have shown that grey matter atrophy is more pronounced in MS patients with cognitive impairment vs. those without (Amato et al., 2006), and that the topographical distribution of such damage differs between patients with RRMS and the chronic forms (Bobholz & Rao, 2003; Morgen et al., 2006; Roosendaal et al., 2011; Zakzanis, 2000).

In MS, there are periventricular white matter alterations within the deep white matter of the frontal lobes and around the corpus callosum independent of disease subtype (Kutzelnigg et al., 2005). As a result, some similarities in the cognitive

profiles of different MS disease courses have been noted (Chiaravalloti & DeLuca, 2008). However, whereas inflammatory demyelination has traditionally been seen as the main disease process in MS, axonal damage or loss is receiving increasing attention (Trapp & Nave, 2008) since gray matter damage may mainly provide the pathological correlate of the cognitive dysfunction (Bobholz & Rao, 2003; Roosendaal et al., 2011).

The most common pattern of cognitive deficit is seen in three domains - attention/processing speed, memory and executive functions (Chiaravalloti & DeLuca, 2008).

Information processing efficiency refers to the ability to uphold and manipulate information in the brain for a limited time period (Baddeley, 2012) and to the speed of information processing. A reduced speed of processing is frequently reported in MS, regardless of disease subtype (Bergendal et al., 2007; DeLuca et al., 2004; Denney et al., 2005; Janculjak et al., 2002; Olivares et al., 2005; Parmenter et al., 2007). Tests of processing speed can be used to predict long-term cognitive decline, with a pronounced decrease in processing speed occurring over several years of follow-up (Bergendal et al., 2007). As information processing acts as a mediator of performance in a range of cognitively demanding tasks (Ceccarelli et al., 2008; Chiaravalloti & DeLuca, 2008; Lengenfelder et al., 2006) deficits in this cognitive domain seem to be an important limiting factor in cognitive operations (DeLuca et al., 2004).

Long-term memory refers to the ability to learn new information and to recall that information at a later time point (Tulving, 2002). Episodic memory is the type of long-term, declarative memory in which we store memories of personal experiences

that are tied to particular times and places (Tulving, 2002). Episodic memory is one of the most consistently impaired cognitive functions in MS and is seen in 40–65% of patients (Bobholz & Rao, 2003; Rao et al., 1991). In contrast to early work on memory impairment in MS that proposes retrieval deficits as the primary cause for the memory deficit (Rao et al., 1989; Thornton et al., 2002) it seems that the initial learning (i.e. encoding) of information is the core problem (DeLuca et al., 1994; DeLuca et al., 1998; Thornton et al., 2002). This deficit in learning new information seems to affect prospective memory abilities (Rendell et al., 2007) and results in poor decision-making abilities (Nagy et al., 2006). Several factors have been associated with poor learning abilities in people with MS, including slow processing speed, difficulties disregarding irrelevant stimuli (i.e. interference), perceptual deficits, and executive dysfunction (Benedict et al., 2002; Defer et al., 2006; Gleichgerrcht et al., 2011; McCarthy et al., 2005; Wachowius et al., 2005). Particularly executive abilities (Gleichgerrcht et al., 2011) - commonly reported to be impaired in people with MS (Benedict et al., 2002; Foong et al., 1997; Wachowius et al., 2005) - are strongly associated with memory impairment in MS as they play an important role in monitoring at both encoding and retrieval (Foong et al., 1997; Gleichgerrcht et al., 2011).

Executive functioning refers to the cognitive abilitiy needed for complex goal-directed behavior and adaptation to environmental changes or demands. This includes the ability to plan, anticipate outcomes, and direct resources appropriately. Deficits in executive functions (i.e. abstract and conceptual reasoning, shifting, inhibition, word fluency, planning, and organisation) occur in about 17% of patients with MS, albeit less frequently than deficits in memory and information processing

efficiency (Bobholz & Rao, 2003; Ceccarelli et al., 2008; Chiaravalloti & DeLuca, 2008).

The proportion of cognitive impairment is in part dependent on MS subtypes (Denney et al., 2005). Possibly due to increased grey matter damage, progressive forms of MS display more pronounced cognitive impairment compared to relapsing-remitting course (Denney et al., 2005). Whereas demyelination and inflammatory activity is pronounced and seems to be the dominant process in RRMS (Kutzelnigg et al., 2005), slowly expanding demyelinating lesions and neurodegenerative events predominate in SPMS and PPMS (Ceccarelli et al., 2008; Kutzelnigg et al., 2005; Roosendaal et al., 2011). Axonal loss and neurodegeneration occur in cortical areas of the brain which are functionally relevant for cognitive processing affecting the cingulated cortex and insular, frontal, and temporal cortices (Ceccarelli et al., 2008; Riccitelli et al., 2011; Roosendaal et al., 2011). Positive associations between the extent of cortical thinning and disease duration indicate that neuropathological changes worsen over time (Bergendal et al., 2007; Smestad et al., 2010) and seem to increase cognitive deterioration in long-term patients with progressive MS subtypes (Bergendal et al., 2007; Smestad et al., 2010).

3 Alzheimer’s disease

3.1 Epidemiology

In 2001, more than 24 million people had dementia, a number that is expected to double every 20 years up to 81 million in 2040 because of the anticipated increase in life expectancy (Ferri et al., 2005). Alzheimer's disease is a progressive neurodegenerative disorder and the most common form of dementia, accounting for 50–60% of all cases (Ferri et al., 2005). The prevalence of AD is below 2 % in individuals aged 60–64 years, but shows an almost exponential increase with age. In consequence, in people aged 85 years or older the prevalence is between 24% and 33% in the western world (Ferri et al., 2005).

With approximately 244.000 incident cases, about 1 million moderately or severely demented people live in Germany thereof 50-70% with AD (Ziegler & Doblhammer, 2009).

3.2 Pathogenesis

It was Alois Alzheimer, who gave a lecture at a congress in Tuebingen, Germany, about the first case of the disease that Kraepelin some years later named Alzheimer’s disease (Möller & Graeber, 1998). In this single case, Alzheimer described distinctive clinical characteristics with memory disturbances and instrumental signs, and the neuropathological changes with plaques and dense bundles of fibrils (tangles), which are today known as the hallmarks of the disease (Dubois et al., 2010) (Figure 12).

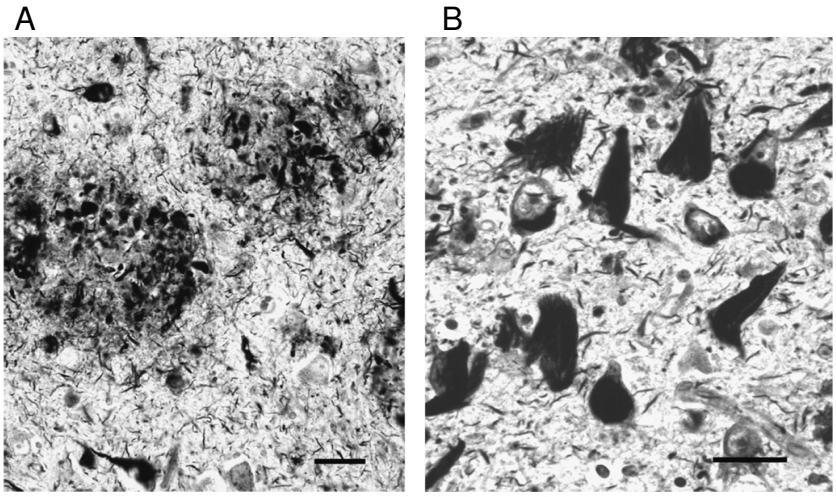

Figure 12. Histopathologic hallmarks of Alzheimer disease demonstrated with Bielschowsky silver impregnation. (A) Neuritic plaques are extracellular fibrillary amyloid deposits, surrounded by swollen, degenerating, argyrophilic neurites. (B) Neurofibrillary tangles are composed of intracellular, insoluble, and protease-resistant fibrillary polymers of tau protein. In both panels, there are wispy argyrophilic neuropil threads. Scale bars = 25 µm. Adapted from Nelson et al. (2009).

Today, these senile or neuritic plaques and neurofibrillary tangles together with a degeneration of the neurons and synapses are hallmarks for Alzheimer's disease (Braak et al., 1999) that were already described by Alzheimer more than 100 years ago. Several pathogenic mechanisms that underlie these changes have been studied, including Amyloid-beta (β) aggregation and deposition with plaque development, tau hyperphosphorylation with tangle formation, neurovascular dysfunction, and other mechanisms such as inflammatory processes, cell-cycle abnormalities, mitochondrial malfunction, and oxidative stress (Hardy, 2006). These neuropathologic accumulations are thought to begin primarily in the medial temporal lobes (e.g., entorhinal cortex, hippocampus). Changes in frontal, temporal, and parietal association cortices occur later (Braak et al., 1999; Braak & Braak, 1991). Eventually, the limbic regions and neocortex are affected (Bobinski et al., 1999; Xu et al., 2000) whereas primary motor and sensory cortices remain relatively spared (Figure 13). Additionally, subcortical neuron loss in the nucleus basalis of Meynert

and locus coeruleus results in decreased levels of cholinergic and noradrenergic markers (Nelson et al., 2009). Consistent with these widespread neuropathologic changes, the primary clinical manifestation of AD is a progressive dementia syndrome that usually begins in later life (Dubois et al., 2007).

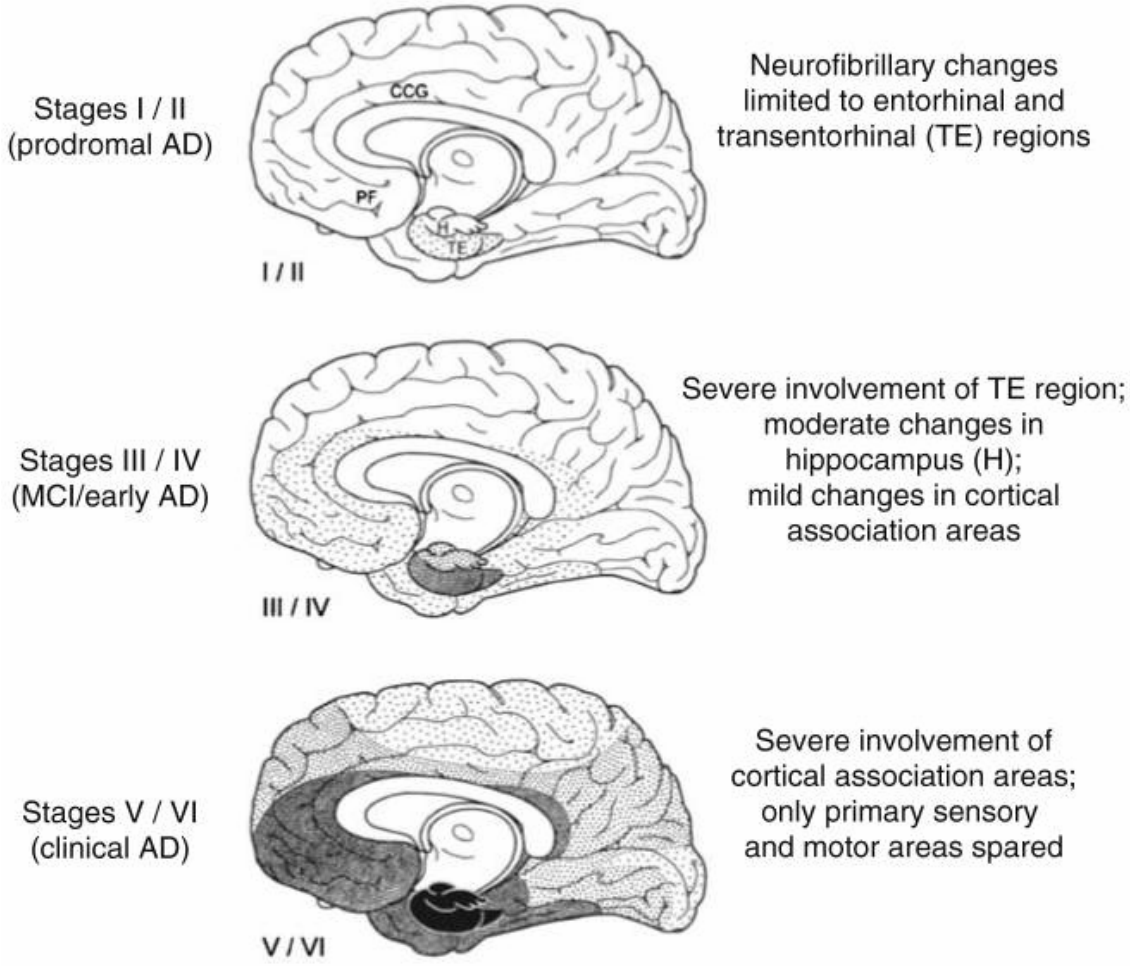

Figure 13. Evolution of neurofibrillary tangle pathology as originally conceived by Braak and Braak (1991). Prior to the appearance of significant clinical symptoms, neurofibrillary changes begin to accumulate in entorhinal and transentorhinal cortex (stages I and II) and may appear surprisingly early in life (e.g., in one's thirties or forties). Increasing involvement of the medial temporal lobe and surrounding association cortices are then thought to coincide with the appearance of mild clinical symptoms (stages III and IV), followed by clinically apparent Alzheimer's dementia and correspondingly severe involvement of medial temporal and cortical association areas (stages V and VI). Adapted from Braak et al. (1999); Braak & Braak (1991).

3.3 Clinical characteristics and diagnosis of Alzheimer's disease

Alzheimer's disease is characterized by a slow progressive loss of cognitive functioning and a long preclinical period during which deficits are observed especially in episodic memory and in several cognitive domains (Dubois et al., 2007; Sperling et al., 2011). As the clinical symptomatology and pathophysiological process of Alzheimer's disease evolve in parallel but temporally offset trajectories they are best conceptualized as a continuum. Specifically, emerging evidence suggests that there may be a latency of a decade or more between the inception of the pathological changes and the onset of clinically significant impairment (Figure 14) (Dubois et al., 2010; Dubois et al., 2007).

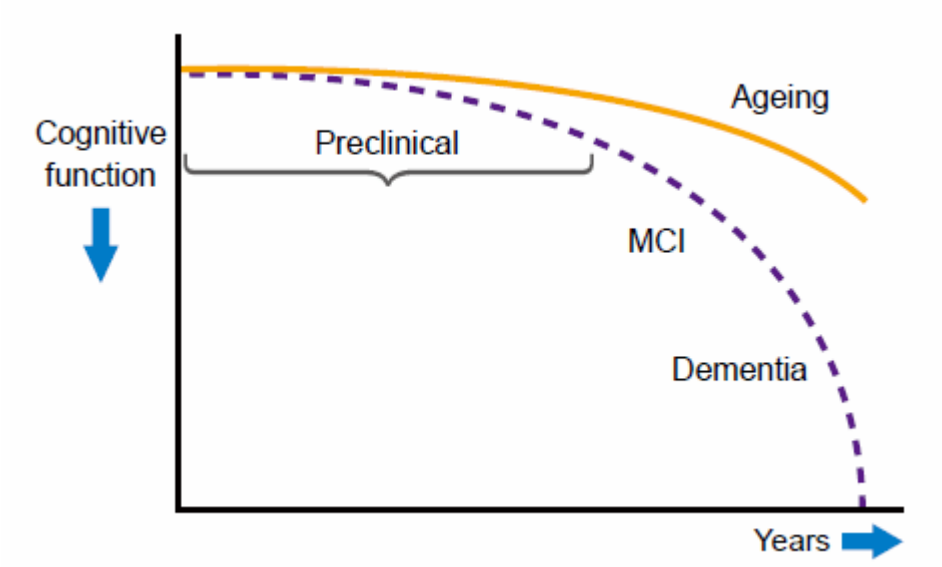

Figure 14. Model of the clinical trajectory of Alzheimer's disease. The stage of preclinical Alzheimer's disease precedes mild cognitive impairment (MCI), and encompasses both asymptomatic individuals in whom the pathophysiological process has already begun but who are clinically indistinguishable from the profile of normal or "typical" aging, as well as individuals who have demonstrated subtle decline from their own baseline that exceeds that expected in typical aging, but would not yet meet criteria for MCI. Adapted from Sperling et al. (2011).

Patients with aMCI, the clinical entity that best represents the pre-dementia stage of Alzheimer's disease (Dubois et al., 2010; Dubois et al., 2007), have

subjective and objective memory impairment whereas activities of daily living are generally normal (Petersen, 2004). Progression to clinically diagnosable AD occurs at a higher rate from mild cognitive impairment (about 10-15% per year) than from an unimpaired state (about 1-2% per year) (Dubois et al., 2007; Petersen et al., 2001).

A diagnosis of probable Alzheimer's disease requires impairment in memory as well as at least one other cognitive domain (e. g. language, executive function, visuo-spatial abilities or global intellectual decline), whilst consciousness remains intact. Impairment affects everyday functioning, represents a decline from previous attainment, onset had been insidious and decline is progressive (American Psychiatric Association, 2000; World Health Organisation, 1993; McKhann et al., 1984).

Evidence from both genetic at-risk cohorts and clinically normal older individuals suggests consistently that the pathophysiological process of Alzheimer's disease begins years, if not decades, prior to the diagnosis of clinical dementia (Dubois et al., 2010; Dubois et al., 2007). Recent advances in neuroimaging, cerebrospinal fluid anlysis, and other biomarkers now provide the ability to detect evidence of neuropathological changes associated with Alzheimer's disease in vivo what is particularly relevant to monitor the preclinical stages of Alzheimer's disease (Figure 15) (Dubois et al., 2010; Dubois et al., 2007; Vemuri & Jack, 2010). However, there exists no established relationship between the manifestation of any specific biomarker and the subsequent appearance of cognitive impairment or interferences with daily self care (Dubois et al., 2010).

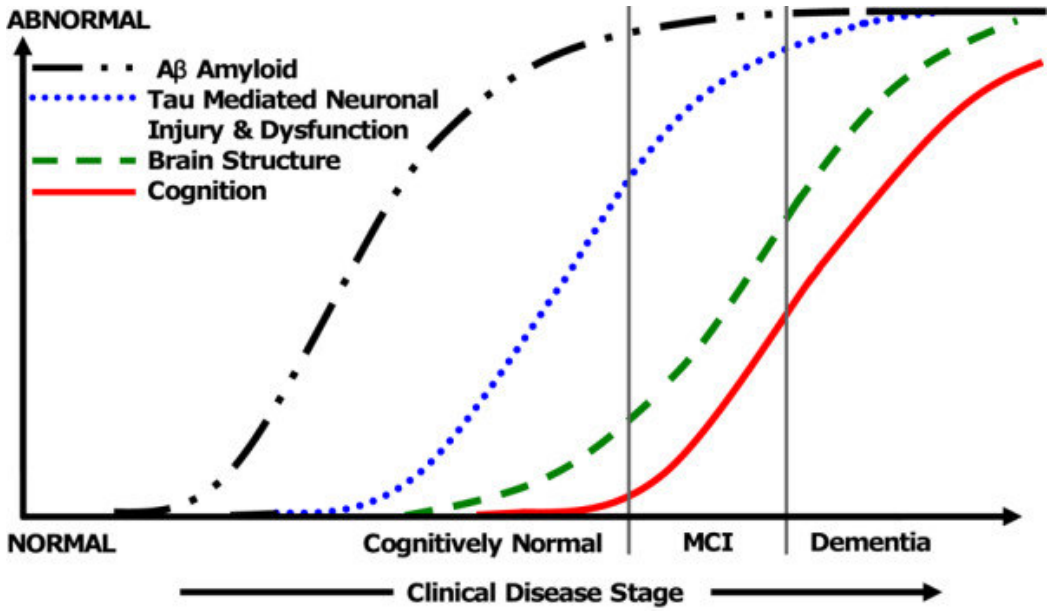

Figure 15. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade, expanded in the preclinical phase. Aβ as identified by CSF Aβ42 assay or PET amyloid imaging. Synaptic dysfunction evidenced by FDG PET or functional MRI, tau-mediated neuronal injury by CSF tau or phospho-tau, brain structure by structural MRI. Biomarkers change from maximally normal to maximally abnormal (y axis) as a function of disease stage (x axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognition and clinical function, are also illustrated. Adapted from Vemuri & Jack (2010).

Nevertheless, upcoming data propose that biomarker confirmation of amyloid-β accumulation and tangle pathology are detectable years prior to meeting criteria for MCI that are linked to functional and structural brain alterations and that predict progression to clinical dementia consistent with Alzheimer's disease (Dubois et al., 2010) (Figure 16).

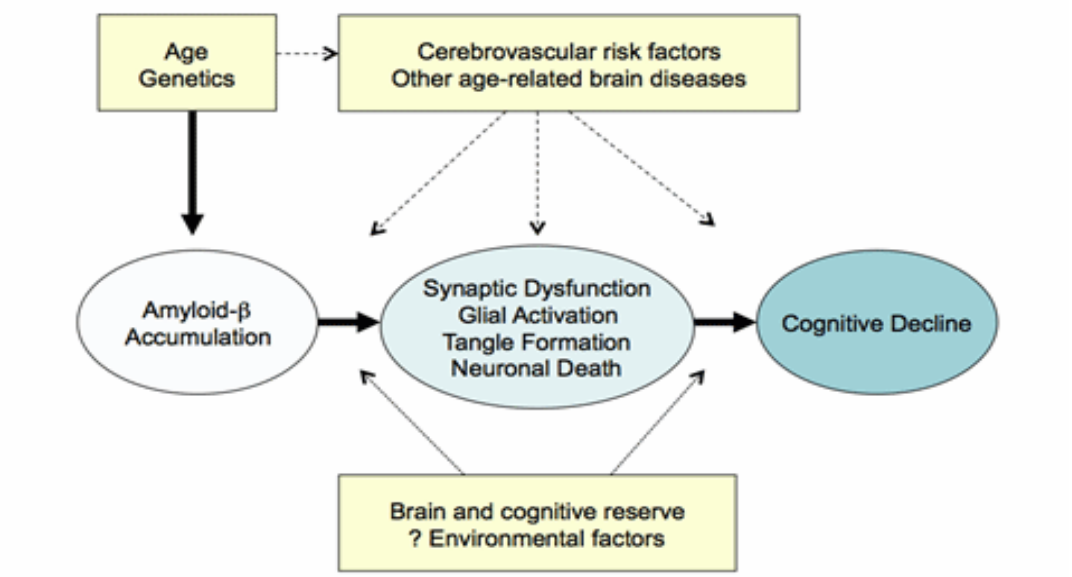

Figure 16. Hypothetical model of the pathophysiological sequence leading to cognitive impairment in Alzheimer's disease. This model postulates that amyloid-β accumulation is an "upstream" event in the cascade that results in synaptic dysfunction, which may lead directly to cognitive impairment and/or trigger "downstream" neurodegeneration and cell loss. Specific host factors, such as brain and cognitive reserve, or other brain diseases may mediate the response to amyloid toxicity and pace of progression towards the clinical manifestations of Alzheimer's disease. Adapted from Sperling et al. (2011).

For research purposes, the diagnosis of Alzheimer's disease is based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) (American Psychiatric Association, 2000) and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA) working group (McKhann et al., 1984). The current DSM-IV criteria (American Psychiatric Association, 2000) include: (a) Memory impairment and at least one additional cognitive impairment; (b) Impaired functioning and functional decline; (c) Gradual onset and continuing cognitive decline; (d) Cognitive deficits not due to other causes. The criteria for Alzheimer's disease suggest that cognitive deficits, functional brain changes, or structural volume loss appear gradually and thus might be identified before the neural degeneration produces clinically diagnosable dementia. Currently, the National Institute on Aging and the Alzheimer's Association

working group has proposed a new diagnostic framework (Albert et al., 2011; Sperling et al., 2011) that anchored around a core clinical phenotype supported by biochemical changes, molecular imaging impairment, brain-structure abnormalities, or genetic mutations associated with Alzheimer's disease. Identifying Alzheimer's disease before irreversible pathological injury would prevent effective intervention on cognition and daily self care is the current neurobiological imperative (McGeer & McGeer, 2001). This new diagnostic framework allows a more specific and earlier diagnosis of Alzheimer's disease than the NINCDS–ADRDA criteria (McKhann et al., 1984) as it considers recent advances in Alzheimer research. Not before the initial identification of a dementia syndrome and the application of criteria based on the clinical features of the Alzheimer's disease phenotype, the new criteria are fulfilled in this two-step diagnostic process. In contrast, the NINCDS–ADRDA clinical criteria of probable Alzheimer's disease do not require evidence of interference with social or occupational functioning but they include the requirements that the onset of Alzheimer's disease is insidious and that there is no other systemic or brain diseases that may account for the progressive memory and other cognitive deficits. The established diagnostic framework yields a probabilistic diagnosis of Alzheimer's disease within a clinical context in absence of a definitive diagnostic biomarker (Dubois et al., 2010; Dubois et al., 2007). According to the NINCDS–ADRDA criteria a definite diagnosis of Alzheimer's disease is only made post mortem when there is histopathological confirmation of the clinical diagnosis (McKhann et al., 1984).

The identification of aMCI as a risk factor for developing AD has stimulated research comparing neuropsychological profiles of both groups to identify similarities and differences in cognitive functioning (Dubois et al., 2010). Episodic memory

impairment is characteristic for both aMCI and AD and is considered as the key early marker in prodromal stages of AD (Dubois et al., 2007). In patients with aMCI episodic memory loss affects both encoding and retrieval which are related to damage at multiple sites of a functionally integrated network comprising the medial temporal lobe, notably the hippocampi (Nestor et al., 2006; Salmon et al., 2008). Insufficient memory recall persisting even under facilitated conditions (i.e. cueing or recognition testing) is a hallmark of this so called hippocampal pattern of memory loss (Dubois et al., 2007) that differentiates patients with prodromal AD from healthy controls with high sensitivity and specificity rates (Buschke et al., 1997).

3.4 Neuropsychology

Memory and learning deficits are the core clinical symptoms of Alzheimer's disease (Dubois et al., 2007). In particular, the loss of memory of events (episodic memory) has been identified as the most frequently observed feature of cognitive dysfunction in AD and is affected early in the disease process (Dubois et al., 2007; Leyhe et al., 2010; Leyhe et al., 2009). Slight declines in episodic memory often occur several years before the emergence of the obvious cognitive and behavioural difficulties that are required for a clinical diagnosis of AD (Dubois et al., 2007; Albert et al., 2001; Backman et al., 2001). Empirical evidence suggests that episodic memory tasks are strong predictors of future AD, because the medial temporal lobes and the hippocampal region - the brain structures indispensable for episodic memory formation (Squire & Alvarez, 1995; Squire et al., 2007; Squire, 2004) - are among the first brain regions affected by the neurodegenerative process of Alzheimer's disease. Clinical tests of episodic memory, such as delayed free recall or recognition, have

become recognized as reliable neuropsychological discriminators between normal aging and early AD and have been proposed as one of the neuropsychological biomarkers for diagnosing Alzheimer's disease at the preclinical MCI stage (Dubois et al., 2007). The episodic memory deficits are seen to be caused by impaired encoding, storing (consolidating) and to a lesser degree retrieval of memory (Twamley et al., 2006) as illustrated in memory tests where subjects with Alzheimer's disease show episodic memory impairment without cueing-related improvement (Carlesimo et al., 2011; Grober et al., 2010).

Semantic memory is also affected in AD (Chertkow et al., 2008). Patients with Alzheimer's disease can be affected by semantic memory disorders leading to semantic paraphasias,, difficulties in object naming tasks (Chertkow et al., 2008; Salmon & Bondi, 2009), or low production of items from a given phonematic or semantic category on timed verbal fluency tasks (Salmon & Bondi, 2009). Despite the indisputable evidence of semantic deficits in Alzheimer's disease, questions related to the nature of these interferences have not been adequately answered. Up to now it is not yet clear whether the semantic deficit stems from a loss of information in the semantic store (Chertkow et al., 2008; Salmon & Bondi, 2009) or is related to a disturbance to access and manipulate semantic information (Chertkow et al., 2008; Salmon & Bondi, 2009).

Executive dysfunction has traditionally been associated with subcortical and frontal diseases; however, it is also impaired early in AD (Baudic et al., 2006; Collie & Maruff, 2000). Several studies have demonstrated that dysexecutive symptoms go along with AD already in the early stages of the disease, emerging in parallel with episodic memory dysfunction but usually before the onset of significant deterioration

of visuospatial and language abilities (Baudic et al., 2006; Collie & Maruff, 2000). It has been argued that many of the early exertions experienced by patients even in the early phase of AD in performing everyday activities due to executive dysfunction (Perry & Hodges, 1999). There is common agreement regarding the early onset of impairments in executive abilities (e.g. inhibition, task-switching, and concurrent manipulation of information) although it remains controverstial whether all executive functions are affected in parallel or whether it is domain dependent (Baudic et al., 2006; Perry & Hodges, 1999) as some studies detected early deficits in concept formation and reasoning in very mild AD whereas other executive abilities were intact (Baudic et al., 2006; Collie & Maruff, 2000). Even though engagement of attention appears to be relatively spared, difficulties in shifting attention back and forth from a task or object to another and can be objectified in course of the disease, reflecting supervisory control and response inhibition malfunction (Collie & Maruff, 2000; Metzler-Baddeley, 2007; Perry & Hodges, 1999; Perry et al., 2000). Attention shifting problems have been demonstrated in tests involving the recognition of overlapping line drawings and in tests requiring selective focus on local or global visual features, and specific abnormalities in the response to visual cues have also been reported (Perry & Hodges, 1999).

Impairment in visual processing can also be detected in the early stages of the disease, both in visuospatial ability and object recognition manifesting as construction, drawing, and orientation impairments (Collie & Maruff, 2000; Guerin et al., 2002). The ‘‘closing-in’’ phenomenon, that is the tendency to copy a figure very closely or even within the given model, is a subtype of constructional apraxia that appears to have good specificity for AD with respect to other dementias (Kwak,

2004). Overall, constructional apraxia in early stage predicts rapid cognitive decline (Guerin et al., 2002; Smith et al., 2001).

Summarizing, in most cases, even at the earliest stages of Alzheimer's disease, the memory disorder is associated with other cognitive changes, albeit aMCI should be considered as a high-risk syndrome for progression to AD (Dubois et al., 2007).

4 Similar Autobiographical memory impairment in long-term secondary progressive multiple sclerosis and Alzheimer's Disease

4.1 Introduction

Autobiographical memory (AM) is a mental representation of personal events and data that allows for the retrieval of personal semantic "facts" (e.g. date and place of wedding) and the recollection of specific events from our past (episodic memory; e.g. the situation of one's wedding ceremony).

The neuroanatomical substrates of AM include the posterior cingulate cortex; the medial temporal lobe (including the hippocampus); the medial prefrontal cortex; and the inferior parietal lobe. The role of the medial temporal lobe and hippocampus on AM encoding and retrieval is still under debate, even with respect to the recollection of recent and remote memories (Svoboda et al., 2006).

The standard model of consolidation (Alvarez & Squire, 1994) suggests a temporary dependency on medial temporal lobe and hippocampal structures for formation and consolidation of declarative knowledge. After the consolidation process remote memories are stored in the neocortex and the hippocampus is no longer required for the retrieval of these memories. By contrast, the Multiple Trace Theory (Nadel & Moscovitch, 1997) proposes that the hippocampal formation encodes all information and forms memory traces that include both hippocampal and neocortical neurons. In this model, each time a memory is retrieved, a new hippocampally mediated trace is created. Thus, frequently repeated remote memories are

represented by more and stronger hippocampal–neocortical traces than recent memories, making them less susceptible to disruption by brain damage (Nadel & Moscovitch, 1997).

Several studies have examined AM in amnesic syndromes (Kopelman et al., 2009) and degenerative dementias (Nestor et al., 2002). AM impairment is one of the most apparent symptoms in Alzheimer´s disease (Meeter et al., 2006), where there is a pattern of retrograde amnesia that follows Ribot's Law (Ribot, 1881) such that older memories are better preserved than more recent ones. Even patients with aMCI exhibit deterioration of AM, including personal incident memory and personal semantic data that follows a temporal gradient (Leyhe et al., 2009). As the presence of aMCI is a risk factor for developing AD (Gauthier et al., 2006), AM impairment in MCI may signal the onset of hippocampal dysfunction associated with neurodegenerative (Alzheimer´s disease-related) pathology (Leyhe et al., 2009).

MS is characterized by the appearance of widespread lesions and plaques in the brain and spinal cord. These lesions and plaques affect the myelin sheath, thus impairing axonal propagation of the action potential (Minagar et al., 2004). While inflammatory demyelination has traditionally been seen as the main disease process in MS, axonal damage or loss is receiving increasing attention (Trapp & Nave, 2008). Gray matter damage may be the pathological correlate of the cognitive dysfunction that arises in 40-70% of MS patients (Bobholz & Rao, 2003).

The topography of grey matter atrophy in MS differs among the MS subtypes: RRMS, SPMS, and PPMS (Riccitelli et al., 2011). Whereas demyelination and inflammatory activity is pronounced and seems to be the dominant process in RRMS (Kutzelnigg et al., 2005), slowly expanding demyelinating lesions and

neurodegenerative events predominate in SPMS and PPMS (Ceccarelli et al., 2008; Kutzelnigg et al., 2005; Roosendaal et al., 2011). Axonal loss and neurodegeneration occur in cortical areas involved in cognitive processing (Ceccarelli et al., 2008; Riccitelli et al., 2011) and seem to increase cognitive deterioration in long-term patients with progressive MS subtypes (Bergendal et al., 2007; Smestad et al., 2010).

Various aspects of cognitive functioning are affected in MS (Rao et al., 1991) but only a few studies have examined MS-related AM dysfunction (Kenealy et al., 2002; Paul et al., 1997). Kenealy et al. (Kenealy et al., 2002) found poorer performance on the autobiographical incident schedule of the AMI (Kopelman et al., 1989) than in the retrieval of personal semantic information in elderly MS patients. They also found a temporal gradient in autobiographical episodic memory, with better preservation of memory for remote than for recent incidents. By contrast, Paul et al. (Paul et al., 1997), found an impairment of memory for personal semantic information but not autobiographical incident memory as assessed with the AMI (Kopelman et al., 1989) in a sample of MS patients with average disease duration of 11 years. They did not find a temporal gradient in the retrieval of either personal semantic information or autobiographical incidents.

Cortical thinning varies regionally in patients with SPMS and is most prominent in areas of the brain that have extensive cortico-cortical connections (Ceccarelli et al., 2008; Riccitelli et al., 2011; Roosendaal et al., 2011). These areas play an important role in AM storage and retrieval (Svoboda et al., 2006). Similarly, brain regions involved in AM seem to be affected by the process of gray matter atrophy in patients with AD (Meulenbroek et al., 2010).

In the present study we compared AM retrieval in an education- and gender-matched sample of healthy controls and patients with aMCI, early AD, RRMS, or SPMS, using the AMI (Kopelman et al., 1989). As neurodegeneration occurs in similar cortical areas in (pre)dementia and progressive MS, we hypothesized that SPMS patients would exhibit a graded loss of AM akin to that seen in patients with early AD or aMCI. We predicted that patients with RRMS, in which inflammatory activity and demyelination dominate (Kutzelnigg et al., 2005) and primarily affect speed of information processing (Denney et al., 2004), would exhibit normal AM similar to that of HC participants.

4.2 Methods

4.2.1 Participants

There were 112 participants in this study, including 67 females and 45 males, with a mean age of 65.9 ± 9.4 years. All groups had an n of 20 except SPMS, which comprised 32 patients. All participants had normal or corrected-to-normal visual acuity and sufficient hearing ability. None of the participants had a physical handicap that affected his or her ability to perform the required tasks, nor any indication of neurological or psychiatric disorders unrelated to his or her diagnosis. The local ethical committee of the University Hospital of Tübingen approved the study. All participants signed an informed consent form after receiving a detailed explanation of the study.

4.2.1.1 Patients with aMCI or AD

Patients with aMCI or AD were recruited from the Memory Clinic of the Department of Psychiatry and Psychotherapy of the University Hospital of Tübingen. They underwent physical, neurological, neuropsychological, and psychiatric examinations, as well as brain imaging. Routine laboratory tests included Lues (syphilis) serology as well as analysis of vitamin B12, folic acid, and thyroid-stimulating hormone levels.

The diagnosis of aMCI was defined by the Mayo criteria (Petersen et al., 1999), which includes the presence of a memory complaint (corroborated by an informant), objectively impaired memory function, preserved general cognitive function, intact activities of daily living, and the absence of dementia. All AD patients met diagnostic criteria of probable AD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 2000).

4.2.1.2 Patients with RRMS or SPMS

Fifty-two elderly patients who were under regular follow-up care at the University Hospital Tübingen, Center of Neurology, and who had definite MS according to the McDonald criteria (Polman et al., 2005), participated in this study and were classified as RRMS or SPMS. All underwent a detailed comprehensive neurological examination and were scored accordingly on the EDSS (Kurtzke, 1983). The EDSS is a method to quantify disability in patients with MS. Eight functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other) are scored on an ordinal clinical rating scale ranging from 0 (normal

neurological examination) to 10 (death due to MS) in half-point increments (Kurtzke, 1983).

4.2.1.3 Healthy control group

HC individuals did not have a history of neurological or psychiatric disease or any sign of cognitive decline, as confirmed by a clinical interview.

4.2.2 Neuropsychological assessment

All participants underwent neuropsychological assessment of global cognition (Mini-Mental State Examination [MMSE]) (Folstein et al., 1975), executive functions (Trail Making Test Part B) (Reitan, 1958), and verbal learning and memory (CERAD word list immediate and delayed recall; word list recognition) (Morris et al., 1989). Episodic memory was assessed by verbal learning of ten words over three trials as well as recall and recognition of the ten-word list. Trail Making Test part B includes numbers (1 – 13) and letters (A – L) which must be connected in an ascending alternating pattern (i.e., 1-A-2-B-3-C, etc.) as fast as possible. As the subjects have to switch between mental sets the Trail Making Test B is used to assess cognitive flexibility and reflects executive functions (Chen et al., 2009).

All participants took part in the AMI (Kopelman et al., 1989). The AMI is a semi-structured interview consisting of two parts that independently test recall for the two components of AM, autobiographical incidents and personal semantic information. The personal semantic schedule requests facts from childhood, early adult life, and recent years (i.e. the last 5 years before test administration). For each

time period, a maximum of 21 points can be achieved. The autobiographical incident questionnaire requests personal experiences of the same three time periods. For each time period, the maximum score is nine.

4.2.3 Data analysis

The SPSS-16 statistical package for Windows was used for data analysis. For all tests, the level of significance was set to $p < .05$. Levene's test was used to assess homogeneity of variance. Differences in age, education, global cognition, anterograde memory (verbal learning, recall and recognition) and frontal/executive functions were assessed using a one-way analysis of variance (ANOVA) followed by a post hoc Tukey test. Independent samples t-test was used to detect differences among the MS subgroups in years since diagnosis. We applied the Pearson chi-square test to detect group differences in gender distribution and the nonparametric Mann-Whitney U test to detect group differences among the MS subgroups in the EDSS scores. We used two-way ANOVAs with group and time period as factors to examine semantic and episodic autobiographical memory recall. We examined between-group differences within each time period using a one-way ANOVA followed by a post-hoc Scheffé test.

To test for a temporal gradient (i.e. better preservation of remote than more recent memories) paired samples t-tests (childhood vs. recent years; childhood vs. early adulthood; early adulthood vs. recent years) within each group were calculated. Results were corrected for multiple comparisons using Bonferroni correction (i.e. comparisons were performed at the $p < .017$ level of significance).

To test for a substantial influence of age on memory recall, we used two-way analyses of covariance with group and time period as factors and age as a covariate to examine semantic and episodic memory recall.

4.3 Results

4.3.1 Clinical and demographic characteristics of the participants

Table 1 presents the clinical and demographic characteristics of the participants. There were no significant group differences in gender distribution (χ^2 [4]=1.194; p=.879) or years of education (F[4,107]=1.058; p=.381). There was a significant group difference in age (F[4,107]=50.297; p < .001). Participants in the RRMS and SPMS groups were younger than those in the HC, aMCI, and AD groups.

The RRMS group scored lower on the EDSS than did the SPMS group. These two groups did not differ in years since diagnosis.

Table 1. Clinical and demographic characteristics of the participants.

	Participant group					Significant differences
	HC	RRMS	SPMS	aMCI	AD	
N	20	20	32	20	20	
Age in years	71.9 (6.5)	57.9 (5.2)	57.8 (5.7)	72.6 (6.8)	73.9 (4.4)	HC = aMCI = AD > RRMS = SPMS [a]
Years of education	13.1 (2.6)	13.9 (2.9)	13.8 (2.7)	13.2 (5.2)	12.6 (3.8)	n.s.
Gender (M/F)	7/13	9/11	15/17	8/12	10/10	n.s.
EDSS score	n/a	3.95 (1.26)	5.09 (1.38)	n/a	n/a	SPMS > RRMS [a]
Years since diagnosis	n/a	12.4 (11.2)	15.3 (9.6)	n/a	n/a	n.s.

Note: Values are expressed as mean (standard deviation).
[a] $p < .001$
HC: healthy controls; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; aMCI: amnesic mild cognitive impairment; AD: early Alzheimer's dementia; M/F = male/female; EDSS: Expanded Disability Status Scale; n/a: not applicable; n.s.: not statistically significant.

4.3.2 Neuropsychological performance on global cognition, anterograde memory and frontal/executive functions

Table 2 presents the neuropsychological performance of the participants on measures of global cognition, anterograde memory (verbal learning, recall and recognition) and frontal/executive functions. There were significant group differences in the MMSE scores ($F[4,107]=64.561$; $p < .001$), word list learning ($F[4,107] = 51.951$; $p < .001$), word list recall ($F[4,107] = 44.715$; $p < .001$), word list recognition ($F[4,107] = 35.629$; $p < .001$), and Trail Making Test part B ($F[4,107] = 38.860$; $p < .001$).

MMSE scores in the AD group were lower than those in the RRMS, SPMS, and aMCI groups, which did not differ. Verbal learning was worst in patients with AD compared to the RRMS/SPMS groups but did not differ from that of patients with aMCI. Word list recall was mostly impaired in patients with AD compared to patients with RRMS, SPMS, and aMCI where no differences could be detected. Word list recognition was similar in patients with RRMS and SPMS and better compared to patients with aMCI and AD that were in turn worse than patients with aMCI. Time to complete Trail Making Test B was longest (i.e. indicating greater impairment) in patients with AD and SPMS compared to patients with aMCI and RRMS. In all tests the HC group performed better than the patient groups.

Table 2. Cognitive performance of the individual groups on measures of global cognition, anterograde memory and frontal/executive functions.

	Participant group					Significant differences
	HC	RRMS	SPMS	aMCI	AD	
N	20	20	32	20	20	
MMSE score max. 30 points	29.7 (0.50)	26.2 (1.70)	26.1 (1.60)	26.7 (1.03)	21.5 (2.60)	HC > RRMS = SPMS = aMCI [c] > AD [c]
Word List Learning max. 30 words	22.1 (2.29)	15.1 (2.56)	13.7 (2.41)	12.9 (2.28)	10.6 (2.32)	HC > RRMS, SPMS, aMCI, AD [c] RRMS [c], SPMS [b] > AD
Word List Recall max. 10 words	8.1 (1.26)	4.3 (1.38)	3.4 (2.19)	3.9 (1.50)	1.4 (1.31)	HC > RRMS, SPMS, aMCI, AD [c] RRMS = SPMS = aMCI > AD [c]
Word List Recognition % correct	98.7 (2.75)	91.1 (10.20)	88.2 (9.56)	75.5 (14.2)	61.8 (14.44)	HC > aMCI [c], AD [c], SPMS [a] RRMS = SPMS > aMCI [c] > AD [a]
Trail Making Test B time in sec.	91.7 (16.03)	160.1 (15.32)	227.3 (16.68)	126.1 (27.8)	234.6 (18.23)	SPMS = AD > RRMS, aMCI > HC [c]

Note: Values are expressed as mean (standard deviation).
[a] $p < .05$; [b] $p < .01$; [c] $p < .001$
HC: healthy controls; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; aMCI: amnesic mild cognitive impairment; AD: early Alzheimer's dementia; N: number of participants; MMSE: Mini Mental State Examination; max.: maximum.

4.3.3 Autobiographical episodic memory

Table 3 presents the autobiographical episodic memory AMI scores in all groups. We found a significant main effect of time period ($F[2,214]=43.070$; $p < .001$) and group ($F[4,107] = 21.444$; $p < .001$). Overall, the AD group performed more poorly than did the other groups. The HC and RRMS groups performed similarly to one another, as did the SPMS and aMCI groups. The HC/RRMS scores were higher than the SPMS/aMCI scores.

Whereas recall of autobiographical incident memories for childhood, early adulthood and recent life was similar in HC and patients with RRMS, patients with SPMS, aMCI and AD were affected dependent on time period (significant group x time period interaction: $F[8,214]=6.021$; $p < .01$). Recall of autobiographical incident memories from childhood was poorer in the AD group than in all other groups, which did not differ from one another. Recall of autobiographical incident memories from early adulthood was poorer in the AD group than in the HC, RRMS, and aMCI groups, which did not differ from one another, and poorer in the SPMS group than in the HC group. There were no other significant group differences. Recall of autobiographical incident memories from recent life was poorer in the AD group than in all other groups; poorer in the aMCI group than in the HC group; and poorer in the SPMS group than in the RRMS and HC groups. There were no other significant group differences.

Paired t-tests showed that temporal gradients (i.e. better preservation of remote than more recent memories) could be found in patients with AD, aMCI, and SPMS. In the aMCI/AD group, recall of autobiographical incident memories from childhood and early adulthood was better than from recent life. In the SPMS group, recall of autobiographical incident memories from childhood was better than from early adulthood and recent life. In contrast, in patients with RRMS and the HC group, recall of autobiographical incident memories from childhood, early adulthood, and recent life was similar. Figure 17 illustrates the episodic autobiographical memory performance of the individual groups.

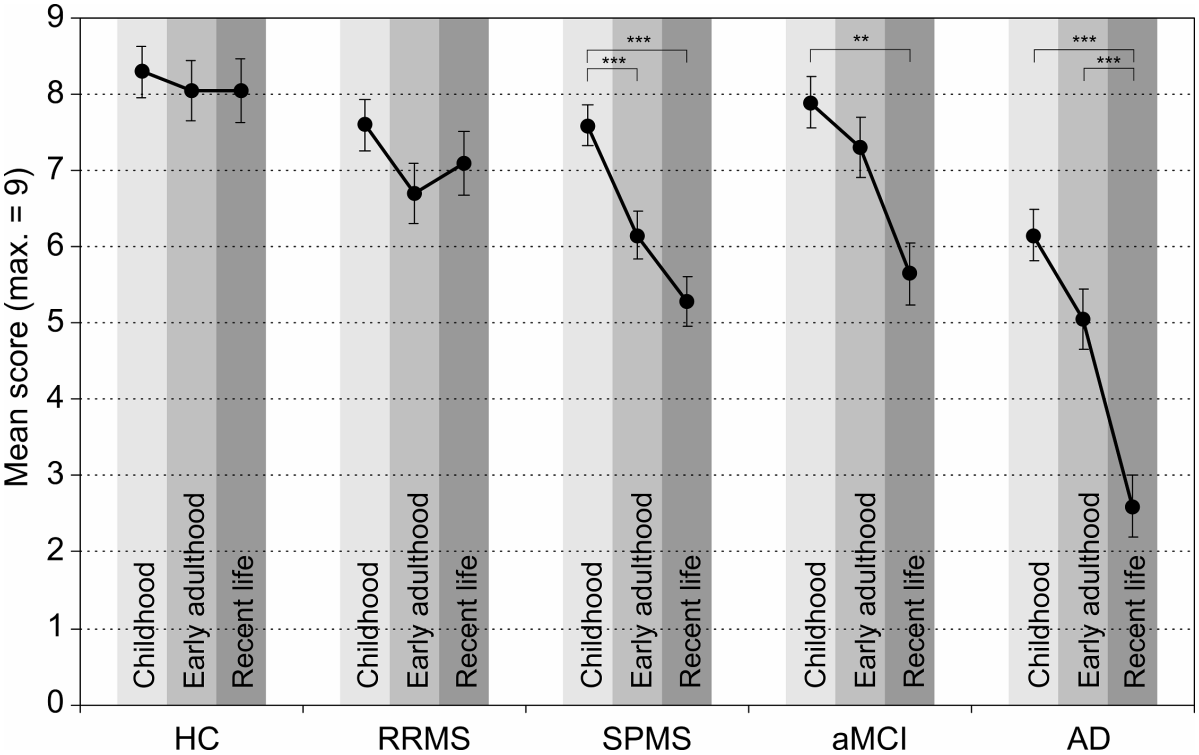

Figure 17. Recall of personal incident memories across life periods in healthy controls (HC), patients with relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), amnesic mild cognitive impairment (aMCI), and early Alzheimer's dementia (AD) patients. Means and standard errors of means are given; max. = maximum. ** $p < .01$; *** $p < .001$.

Within each time period there was no main effect of the covariate factor age: childhood ($F[1,35]=1.185$; $p=.324$); early adulthood ($F[1,35]=0.745$; $p=.797$); recent life ($F[1,35]=1.519$; $p=.128$).

Table 3. Autobiographical episodic memory as revealed by scores on the Autographical Memory Interview (AMI) (Kopelman et al., 1989).

Participant group	Time period			Significant differences
	Childhood	Early adulthood	Recent life	
HC	8.30 (1.03)	8.05 (1.05)	8.06 (1.31)	n.s.
RRMS	7.60 (1.19)	6.70 (1.84)	7.10 (1.37)	n.s.
SPMS	7.59 (1.21)	6.16 (1.63)	5.28 (1.42)	childhood > recent life [c] childhood > early adulthood [c]
aMCI	7.90 (1.25)	7.30 (1.45)	5.65 (2.81)	childhood > recent life [b]
AD	6.15 (2.51)	5.05 (2.52)	2.60 (2.11)	childhood > recent life [c] early adulthood > recent life [c]
Significant differences	AD < HC [c] AD < RRMS [a] AD < SPMS [a] AD < aMCI [b]	AD < HC [c] AD < RRMS [a] AD < aMCI [b] SPMS < HC [b]	AD < HC [c] AD < RRMS [c] AD < SPMS [c] AD < aMCI [c] SPMS < HC [c] SPMS < RRMS [b] aMCI < HC [b]	

Note: Values are expressed as mean (SD). The maximum score is nine points.
[a] $p < .05$; [b] $p < .01$; [c] $p < .001$
HC: healthy controls; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; aMCI: amnesic mild cognitive impairment; AD: early Alzheimer's dementia; n.s.: not statistically significant.

4.3.4 Autobiographical semantic memory

Table 4 presents the autobiographical semantic memory AMI scores in all groups. We found a significant main effect of time period ($F[2,214]=10.453$; $p < .001$) and group ($F[4,107] = 15.532$; $p < .001$). Overall, the AD group performed more poorly than did the other groups, which did not differ from one another.

Whereas recall of semantic memories for childhood, early adulthood and recent life was similar in HC and the RRMS/SPMS groups, patients with aMCI and AD were affected dependent on time period (significant group x time period interaction: $F[8,214]=10.156$; $p < .001$). Recall of semantic memories from early

adulthood and recent life was poorer in the AD group than in all other groups. Recall of semantic memories from recent life was poorer in the aMCI group than in the RRMS, SPMS, and HC groups, which did not differ from one another.

Paired t-tests showed that temporal gradients (i.e. better preservation of remote than more recent memories) could be found in patients with AD and aMCI but, in contrast to autobiographical episodic memory not in patients with SPMS. In the AD group, recall of semantic memories from childhood was better than from early adulthood, which in turn was better than from recent life. In the aMCI group, recall of semantic memories from childhood and early adulthood was better than from recent life. In the RRMS, SPMS, and HC groups recall of semantic memories from childhood, early adulthood, and recent life was similar.

Figure 18 illustrates semantic autobiographical memory performance of the individual groups.

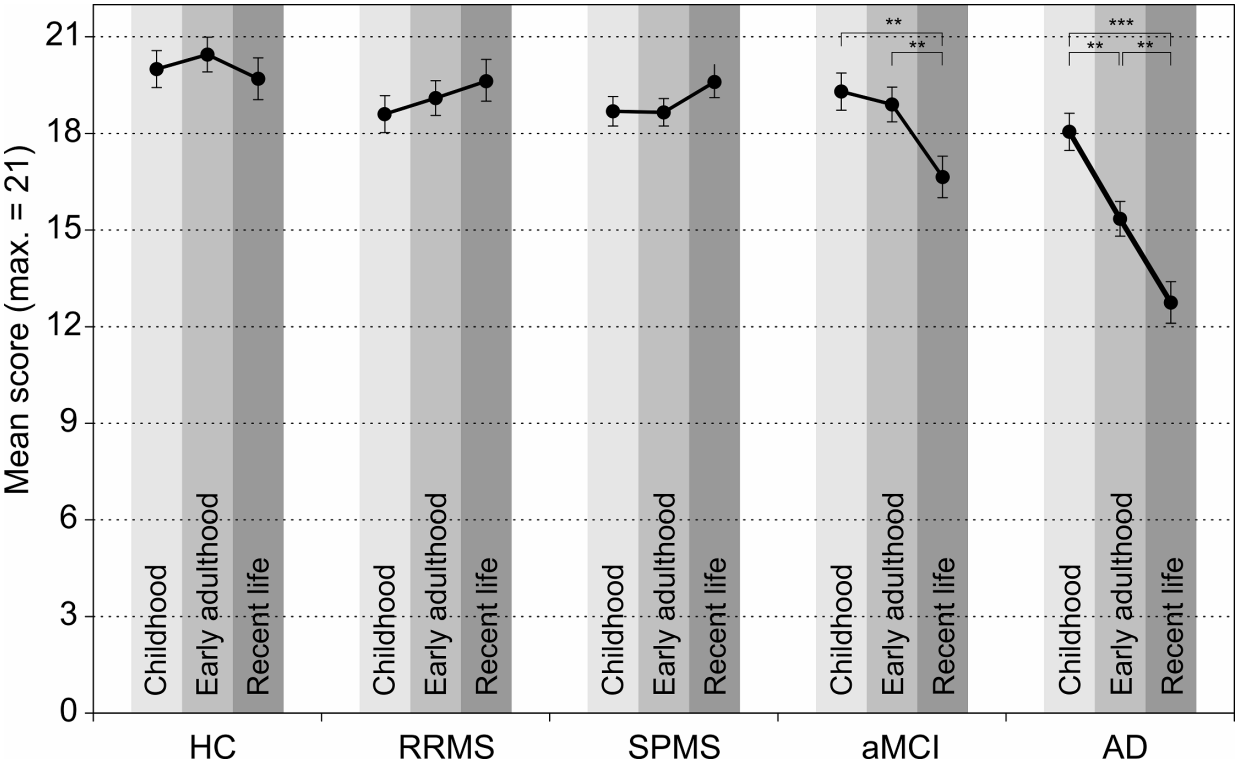

Figure 18. Recall of personal semantic memories across life periods in healthy controls (HC), patients with relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), amnesic mild cognitive impairment (aMCI), and early Alzheimer's dementia (AD) patients. Means and standard errors of means are given; max. = maximum. ** $p < .01$; *** $p < .001$

Within each time period there was no main effect of the covariate factor age: childhood ($F[1,35]=6.906$; $p=.588$); early adulthood ($F[1,35]=1.190$; $p=.320$); recent life ($F[1,35]=1.347$; $p=.210$).

Table 4. Autobiographical semantic memory as revealed by scores on the Autographical Memory Interview (AMI) (Kopelman et al., 1989).

Participant group	Time period			Significant differences
	Childhood	Early adulthood	Recent life	
HC	20.00 (1.86)	20.45 (0.94)	19.70 (1.86)	n.s.
RRMS	18.30 (2.52)	19.10 (2.17)	19.65 (1.31)	n.s.
SPMS	18.69 (2.87)	18.66 (2.46)	19.63 (1.45)	n.s.
aMCI	19.30 (1.49)	18.90 (1.97)	16.65 (3.86)	childhood > recent life [b] early adulthood > recent life [b]
AD	18.05 (3.45)	15.35 (3.64)	12.75 (4.85)	childhood > early adulthood [b] childhood > recent life [c] early adulthood > recent life [b]
Significant differences	n.s.	AD < HC [c] AD < RRMS [c] AD < SPMS [c] AD < aMCI [c]	AD < HC [c] AD < RRMS [c] AD < SPMS [c] AD < aMCI [c] aMCI < HC [a] aMCI < RRMS [a] aMCI < SPMS [b]	

Note: Values are expressed as mean (SD). The maximum score is 21 points.
[a] $p < .05$; [b] $p < .01$; [c] $p < .001$
HC: healthy controls; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; aMCI: amnesic mild cognitive impairment; AD: early Alzheimer's dementia; n.s.: not statistically significant.

4.4 Discussion

We investigated AM retrieval among elderly patients with RRMS and SPMS vs. an education- and gender-matched sample of aMCI patients, early AD patients, and healthy controls. Patients with SPMS but not RRMS exhibited graded loss of personal incident memory akin to that seen in patients with early AD or aMCI. However, there were no differences in personal semantic data retrieval in patients with SPMS, patients with RRMS, or HC participants. These neuropsychological results point at distinct disease mechanisms in different MS subtypes. In patients with

long-term SPMS AM impairment might be due to neurodegeneration in brain areas that are functionally relevant for AM encoding and retrieval.

SPMS patients had difficulty recalling personal incidents from early adulthood and recent life as compared to HC participants. This pattern of autobiographical incident memory decline resembles qualitatively that seen in patients with aMCI or AD, where structures of the medial temporal lobe, including the hippocampus, are affected in the early stages of the disease (den Heijer et al., 2010). Prior investigations on AM retrieval in patients with aMCI or AD indicate that AM relies on hippocampal integrity (Leyhe et al., 2009). AM retrieval deficits appear to coincide with consolidation disturbances related to functional impairment in the medial temporal lobe and hippocampus (Nadel & Moscovitch, 1997). Similar to aMCI and AD patients, in SPMS patients these brain regions seem to be affected by the gray matter atrophy (Ceccarelli et al., 2008; Riccitelli et al., 2011; Roosendaal et al., 2011). These neurodegenerative processes become progressively more severe in long-term patients with progressive MS subtypes (Bergendal et al., 2007; Smestad et al., 2010).

According to the standard model of memory consolidation (Alvarez & Squire, 1994), formation and consolidation of declarative knowledge depends on neocortical regions including medial temporal lobe and the hippocampus, but only for a limited time period. Observations of a temporal gradient in memory performance resulting from hippocampal damage or atrophy have led to the hypothesis that the hippocampus participates only in memory consolidation processes (Alvarez & Squire, 1994), and at the completion of these processes, memories are stored in the neocortex where they become resistant to hippocampal disruption. Hippocampal

lesions are seen in SPMS patients, and the extent of hippocampal damage depends on disease progression (Sicotte et al., 2008). Disturbed consolidation of autobiographical information should not affect remote memories. This accounts for the observed temporal gradient in our patients.

Consistent with our hypothesis, we did not observe substantial memory loss for autobiographical incidents or facts in the RRMS group. RRMS involves primarily inflammatory activity and is characterized by focal pathology of white matter (Kutzelnigg et al., 2005). Gray matter loss is seen mainly in the right precentral and postcentral gyri (Ceccarelli et al., 2008), putamen, corpus callosum, and cingulate sulcus (Pagani et al., 2005); thus, regions involved in AM are relatively spared. Hippocampal degeneration is observable in RRMS, but differs from that seen in SPMS. RRMS is characterized by selective loss of volume in the cornu ammonis 1 region of the hippocampus, whereas SPMS is characterized by loss of volume in cornu ammonis 1 and other cornu ammonis regions (Geurts et al., 2007). Deficits in memory encoding and retrieval accompany loss of volume in hippocampal subregions (Sicotte et al., 2008); hence, our findings might be explained in terms of increased involvement of regions that are functionally relevant for memory storage and retrieval in SPMS as compared to RRMS (Ceccarelli et al., 2008). Additionally, increased neural recruitment during episodic memory retrieval as seen in fMRI studies might account for the better performance in the RRMS group vs. the SPMS group (Bobholz et al., 2006).

Unlike aMCI and early AD patients, SPMS patients exhibited no memory deficits for personal semantic data. Deficits in memory for personal facts associated with Alzheimer´s disease might be due to early disturbance of the lateral temporal

cortex due to neurodegenerative processes (Whitwell et al., 2008; Whitwell et al., 2007). In SPMS this brain region seems to be less affected (Ceccarelli et al., 2008).

In conclusion, this study suggests that distinct disease mechanism associated with MS subtypes lead to differences in AM. We observed graded AM loss in SPMS but not RRMS patients. The temporal gradient in SPMS patients resembles that of aMCI and early AD patients. Our findings could indicate that in long-term SPMS patients AM is affected by neurodegeneration of functionally relevant brain regions.

4.5 Publication

Müller, S., Saur, R., Greve, B., Melms, A., Hautzinger, M., Fallgatter, A., and Leyhe, T. (2012). Similar autobiographical memory impairment in long-term secondary progressive multiple sclerosis and Alzheimer's disease. *Multiple Sclerosis Journal*, 2012 Jun 8 [Epub ahead of print].

5 Recognition performance differentiates between elderly patients in the long term course of secondary progressive multiple sclerosis and amnestic mild cognitive impairment

5.1 Introduction

MS is one of the most common neurological diseases of early and middle adulthood and is characterized by inflammatory demyelination and axonal injury in the brain and spinal cord (Trapp & Nave, 2008). Cognitive impairment is a common symptom of MS, which includes deficits in attention, information processing speed, executive function, working memory, verbal fluency, and episodic memory (Chiaravalloti & DeLuca, 2008). Reported prevalence rates of cognitive impairment in MS range from 43% to 70% (Chiaravalloti & DeLuca, 2008). Cognitive impairment affects MS patients irrespective of disease form (relapsing-remitting vs. progressive) (Chiaravalloti & DeLuca, 2008) and at both the earlier (Duque et al., 2008) and later stages of the disease (Bodling et al., 2009; Smestad et al., 2010).

Inflammatory demyelination traditionally has been seen as the main disease process in MS, but axonal damage or loss is receiving increasing attention (Trapp & Nave, 2008). Whereas demyelination and inflammatory activity are pronounced and seem to be the dominant process in RRMS (Kutzelnigg et al., 2005), regardless of other parameters of disease activity (e.g., relapses or increases in physical disability) (Duque et al., 2008), slowly expanding demyelinating lesions and

neurodegenerative events predominate in progressive forms of MS (Ceccarelli et al., 2008; Kutzelnigg et al., 2005; Roosendaal et al., 2011).

In patients with SPMS neurodegeneration and inflammatory demyelinating lesions occur in areas of the brain which are functionally relevant for cognitive processing (Riccitelli et al., 2011) and worsen over time (Bergendal et al., 2007; Smestad et al., 2010). Several studies show a positive association in SPMS between the extent of cortical thinning and disease duration (Wylezinska et al., 2003). Cognitive deterioration increases in long-term patients with progressive MS (Bergendal et al., 2007; Smestad et al., 2010), with deficits in episodic memory, processing speed, and executive function being especially prominent (Chiaravalloti & DeLuca, 2008).

Episodic memory is first and most severely affected in Alzheimer's disease (Dubois et al., 2007). Deficits in this cognitive domain are the key early marker in prodromal stages of Alzheimer's disease (Dubois et al., 2007), which is characterized by aMCI, with subjects showing memory impairment without cueing-related improvement (Dubois et al., 2010) but preservation of normal activities of daily living (Dubois et al., 2007). Other cognitive domains are less affected in the early stages of AD but deteriorate as AD advances (Dubois et al., 2007). Patients with aMCI who progress to AD show functional disturbances of neuronal connectivity due to atrophy throughout the medial and inferior temporal lobes, temporoparietal association neocortex, frontal lobes, posterior cingulate, and precuneus (Whitwell et al., 2008).

Few studies have examined cognitive impairment in elderly patients with progressive forms of MS (Bodling et al., 2009; Smestad et al., 2010). As advancing age is the most significant risk factor for AD (Hampel et al., 2011), AD-related

pathology cannot be ruled out in elderly MS patients. Therefore, in the present study we aimed to characterize disease-dependent deterioration patterns by comparing age-, education-, and gender-matched groups of elderly patients with SPMS and aMCI using the German version of the CERAD test battery (Barth et al., 2005; Memory Clinic Basel, 2005; Morris et al., 1989). The CERAD test battery is designed to assess a broad array of cognitive (mal)functions (e.g., global cognition, anterograde memory, constructional praxis, speech, mental speed, and executive abilities) associated with AD (Dubois et al., 2010) that are also found in patients with MS (Chiaravalloti & DeLuca, 2008).

Because a recall deficit that does not improve with cueing or recognition is a reliable (neuropsychological) indicator of prodromal AD (Dubois et al., 2007), we hypothesised that aMCI would be characterized by episodic memory loss of the so-called hippocampal type (Dubois et al., 2010), in which learning and retrieval deficits are observed even under facilitated conditions. By contrast, we expected that SPMS would be associated with more global cognitive deficits related to inflammation- and atrophy-induced functional disturbances (Ceccarelli et al., 2008; Roosendaal et al., 2011; Sicotte et al., 2008), including reduced attention and processing speed, impaired executive function (Drew et al., 2009; Wachowius et al., 2005), and deficits in verbal learning and retrieval, but with sparing of recognition ability (Chiaravalloti & DeLuca, 2008).

5.2 Methods

5.2.1 Participants

This study involved 120 participants, including 64 females and 56 males, with a mean age of 60.6 ± 6.4 years. The sample consisted of 40 healthy controls (HC), 40 patients with aMCI, and 40 patients with SPMS. All participants had normal or corrected-to-normal visual acuity and sufficient hearing ability. None of the participants had a physical handicap that affected his or her ability to perform the required tasks, nor any indication of neurological or psychiatric disorders unrelated to his or her diagnosis. To exclude acute symptoms of depression, all participants completed the German version of the revised Beck Depression Inventory (BDI-II, German adaptation) (Hautzinger et al., 2007). The local ethical committee of the University Hospital of Tübingen approved the study. All participants signed an informed consent form after receiving a detailed explanation of the study.

5.2.1.1 Patients with aMCI

Patients with aMCI were recruited from the Memory Clinic of the Department of Psychiatry and Psychotherapy of the University Hospital of Tübingen. All 40 participants underwent physical, neurological, neuropsychological, and psychiatric examinations, as well as brain imaging. Routine laboratory tests included Lues (syphilis) serology as well as analysis of vitamin B12, folic acid, and thyroid-stimulating hormone levels. The diagnosis of aMCI was defined by the Mayo criteria (Petersen, 2004), which include the presence of a memory complaint (corroborated

by an informant), objectively impaired memory function, preserved general cognitive function, intact activities of daily living, and the absence of dementia.

5.2.1.2 Patients with SPMS

Forty elderly patients under regular follow-up care at the University Hospital Tübingen, Center of Neurology, with definite MS according to the revised McDonald criteria (Polman et al., 2011), participated in this study. All underwent a detailed comprehensive neurological examination, were classified as SPMS according to the criteria of Lublin and Reingold (Lublin & Reingold, 1996), and were scored on the EDSS (Kurtzke, 1983). The EDSS is a method to quantify disability in patients with MS. Eight functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other) are scored on a clinical rating scale ranging from 0 (normal neurological examination) to 10 (death due to MS) in half-point increments (Kurtzke, 1983). EDSS scores in our SPMS sample ranged from 2.0 to 7.0, with a mean of 5.2. The mean time since symptom onset was 24.78 ± 12.15 years, and the mean time since diagnosis was 17.88 ± 9.2 years.

5.2.1.3 HC group

HC individuals were selected to match the patient groups in terms of age, gender, and level of education. They had no history of neurological or psychiatric disease and no sign of cognitive decline, as confirmed by a clinical interview.

5.2.2 Neuropsychological assessment

All participants underwent a neuropsychological examination that included the German version of the CERAD test battery (Barth et al., 2005; Morris et al., 1989), the Mini-Mental State examination (MMSE), a 15-item short version of the Boston Naming Test, a semantic word fluency test for animals (1 minute), word list learning (10 words, three trials), word list recall after distraction, word list recognition (10 target and 10 distractor words), figure copying, and delayed figure recall.

The test battery also included the Trail Making Test (part A and B) (Reitan, 1958) and a phonemic fluency task (s-words; 1 minute) (Thurstone, 1938) (CERAD-plus). The Trail Making Test, part A, assesses directed attention and speed of information processing operationalized by connecting as fast as possible the numbers 1–25 in ascending order. The Trail Making Test, part B, includes both numbers (1–13) and letters (A–L) which ought to be connected in an ascending alternating pattern (i.e., 1-A-2-B-3-C, etc.) as fast as possible. As the subjects have to switch between mental sets the TMT-B is used to assess cognitive flexibility. Performance on the Trail Making Test reflects executive function (Reitan, 1958).

For the CERAD-plus test battery normative values for subjects ≥ 49 years, adjusted for age, gender, and education, are provided by the Basel memory clinic (Aebi, 2002).

5.2.3 Data analysis

The SPSS-16 statistical package for Windows was used for data analysis. For all tests, the level of significance was set at $p < .05$. Levene's test was used to assess homogeneity of variance. We compared the groups in terms of age,

education, BDI-II score, and neuropsychological performance (CERAD-plus) using a one-way analysis of variance (ANOVA) followed by a post hoc Tukey test. Bonferroni adjustment was performed to correct for type I errors introduced by the use of multiple tests. To detect group differences in gender distribution, we used the Pearson chi-square test.

The z-scores of the CERAD-plus data were computed by comparing patient data with data from an age-, gender-, and education-matched norm population (N = 1.100; 49-92 years of age; 7-20 years of education) provided by the Basel memory clinic (Aebi, 2002).

We conducted receiver operating characteristic (ROC) curves in order to determine which word list recall and word list recognition scores provide optimal sensitivity and specificity for discriminating SPMS and aMCI.

Pearson correlations between the subscores of the CERAD-plus test battery and age, education, and BDI-II were computed for healthy controls, patients with aMCI and SPMS. Additionally, for patients with SPMS we performed Pearson correlations between the subscores of the CERAD-plus test battery and EDSS scores, time since symptom onset and diagnosis.

To control for the influence of information processing speed and executive function on memory performance in patients with SPMS or aMCI, we computed Pearson correlations between the Trail Making Test (parts A and B) and the episodic memory subscores of the CERAD-plus test battery (i.e., word list learning and delayed recall, word list recognition, delayed figure recall) for patients with SPMS and aMCI.

5.3 Results

5.3.1 Clinical and demographic characteristics of the participants

Table 5 presents the demographic and clinical characteristics of the participants. The groups did not differ in age, education, or gender distribution. We did not detect any acute symptoms of depression (BDI-II).

Table 5. Clinical and demographic characteristics of the participants.

Variables	Participant group			Significant differences
	HC	SPMS	aMCI	
Sample size (n)	40	40	40	
Gender (M/F)	18 / 22	21 / 19	17 / 23	n.s.
Age (years)	60.13 (6.41)	60.78 (4.71)	61.05 (8.02)	n.s.
Education (years)	14.65 (4.12)	14.10 (2.32)	13.65 (2.89)	n.s.
BDI-II score	8.00 (6.03)	8.9 (6.75)	7.13 (3.73)	n.s.

Note: Values are expressed as mean (SD).
HC: healthy controls; SPMS: secondary progressive multiple sclerosis; aMCI: amnestic mild cognitive impairment; M/F: male/female; BDI: Becks Depression Inventory (higher total scores indicate more severe depressive symptoms; maximum 63 points; a cut-off score of 14 indicates mild depression); n.s.: not statistically significant.

5.3.2 Neuropsychological performance

Table 6 presents the means and standard deviations (SDs) of age-, gender-, and education-corrected z-scores of the CERAD-plus subtests.

Table 6. Neuropsychological test results of the CERAD-plus test battery.

Variables	Participant group			Significant differences
	HC	SPMS	aMCI	
Word List Learning	0.01 (0.69)	-1.81 (1.06)	-1.53 (1.09)	HC > SPMS = aMCI[a]
Word List Recall	0.19 (0.75)	-2.19 (0.85)	-2.03 (0.74)	HC > SPMS = aMCI[a]
Word List Recognition	-0.11 (0.69)	-0.54 (0.93)	-2.04 (1.22)	HC = SPMS > aMCI[a]
Word List Intrusion	0.26 (0.76)	-0.05 (0.82)	-0.19 (1.21)	n.s.
Verbal Fluency (animals)	0.31 (0.81)	-1.96 (1.42)	-1.51 (1.23)	HC > SPMS = aMCI[a]
Verbal Fluency (s-words)	0.65 (0.51)	-0.40 (1.18)	-0.25 (1.21)	HC > SPMS = aMCI[a]
Boston Naming Test	0.68 (0.41)	-0.18 (0.96)	0.05 (0.74)	HC > SPMS = aMCI[a]
Constructional Praxis Copy	0.37 (0.72)	-0.58 (1.01)	-0.66 (1.19)	HC > SPMS = aMCI[a]
Constructional Praxis Recall	0.26 (0.84)	-1.83 (0.91)	-1.74 (1.14)	HC > SPMS = aMCI[a]
Trail Making Test, part A	0.18 (0.95)	-1.89 (1.10)	-1.28 (1.05)	HC > SPMS = aMCI[a]
Trail Making Test, part B	0.09 (0.75)	-1.97 (0.83)	-1.03 (0.79)	HC > SPMS = aMCI[a]
MMSE	-0.36 (1.01)	-1.92 (1.23)	-2.35 (0.87)	HC > SPMS = aMCI[a]

Note: Values are mean (age-, gender-, and education-corrected) z-scores (SD). HC: healthy controls; SPMS: secondary progressive multiple sclerosis; aMCI: amnestic mild cognitive impairment; MMSE: Mini Mental Status Examination; n.s.: not statistically significant; [a] significant at a Bonferroni-adjusted significance level of $p < .004$.

Recognition was poorer in aMCI patients than in SPMS patients or HC participants, who performed similarly to one another. After Bonferroni correction we

did not detect any other significant differences among the patient groups. HC participants performed better on global cognition (MMSE), verbal learning and delayed recall, verbal fluency, the Boston Naming Test, and copying and delayed recall of geometric figures (constructional praxis) than did the patient groups. Time to complete the Trail Making Test, parts A and B, was significantly longer (indicating greater impairment) in the SPMS and aMCI groups than in the HC group.

At a z-score of -1.1 in the word list recognition subtest ROC curves provide optimal sensitivity and specificity for discriminating SPMS and aMCI. In this analysis the word list recognition ROC curve accounted for 80.3% of the area under the curve. We obtained a true positive rate of 80.0% in the MCI group and a correct rejection rate of 85.0% in the SPMS group at a z-score of -1.1 in the word list recognition subtest (Figure 19).

With an area under the curve of 58.7 % the word list free recall subtest fails to discriminate patients with SPMS and aMCI with an acceptable sensitivity and specificity rate.

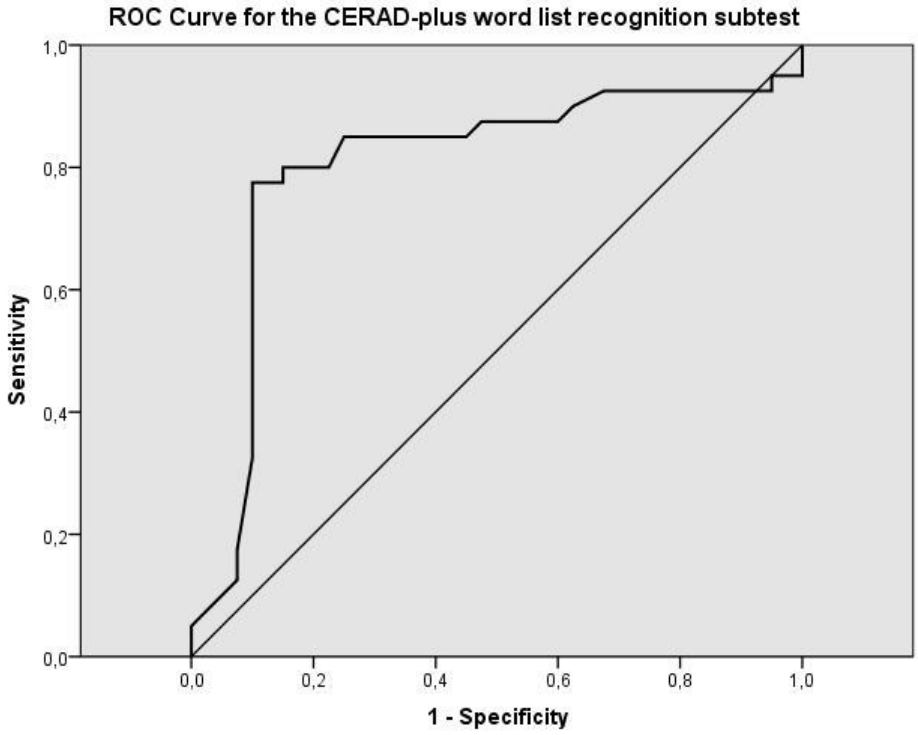

Figure 19. Receiver operating characteristic (ROC) curve based on the word list recognition subtest of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery. The area under the ROC curve was 0.803. The optimal threshold to discriminate patients with secondary progressive multiple sclerosis (SPMS) and amnestic mild cognitive impairment (aMCI) was at a z-score of -1.1, with 80.0% sensitivity and 85.0% specificity.

In patients with SPMS Trail Making Test, part A, correlated significantly with word list learning ($r = .556$; $p < .001$), word list recall ($r = .539$; $p < .001$), and recall of geometric figures ($r = .522$; $p < .01$). We also found significant correlations between scores on the Trail Making Test, part B, and word list learning ($r = .633$; $p < .001$), word list recall ($r = .587$; $p < .001$) and recall of geometric figures ($r = .620$; $p < .001$). There were no significant correlations between scores on the Trail Making Test (part A or B) and the episodic memory subscores of the CERAD-plus test battery in patients with MCI.

In healthy controls, patients with SPMS and aMCI performance on the CERAD-plus subscores did not correlate with age, education, and BDI-II (r's = -.193

to .287; all p's > .5). There were no significant correlations on neuropsychological performance and time since symptom onset, time since diagnosis, or EDSS scores in patients with SPMS (r's = -.238 to .198; all p's > .5).

Figure 20 illustrates the comparisons of the z-scores of the CERAD-plus test battery among the groups.

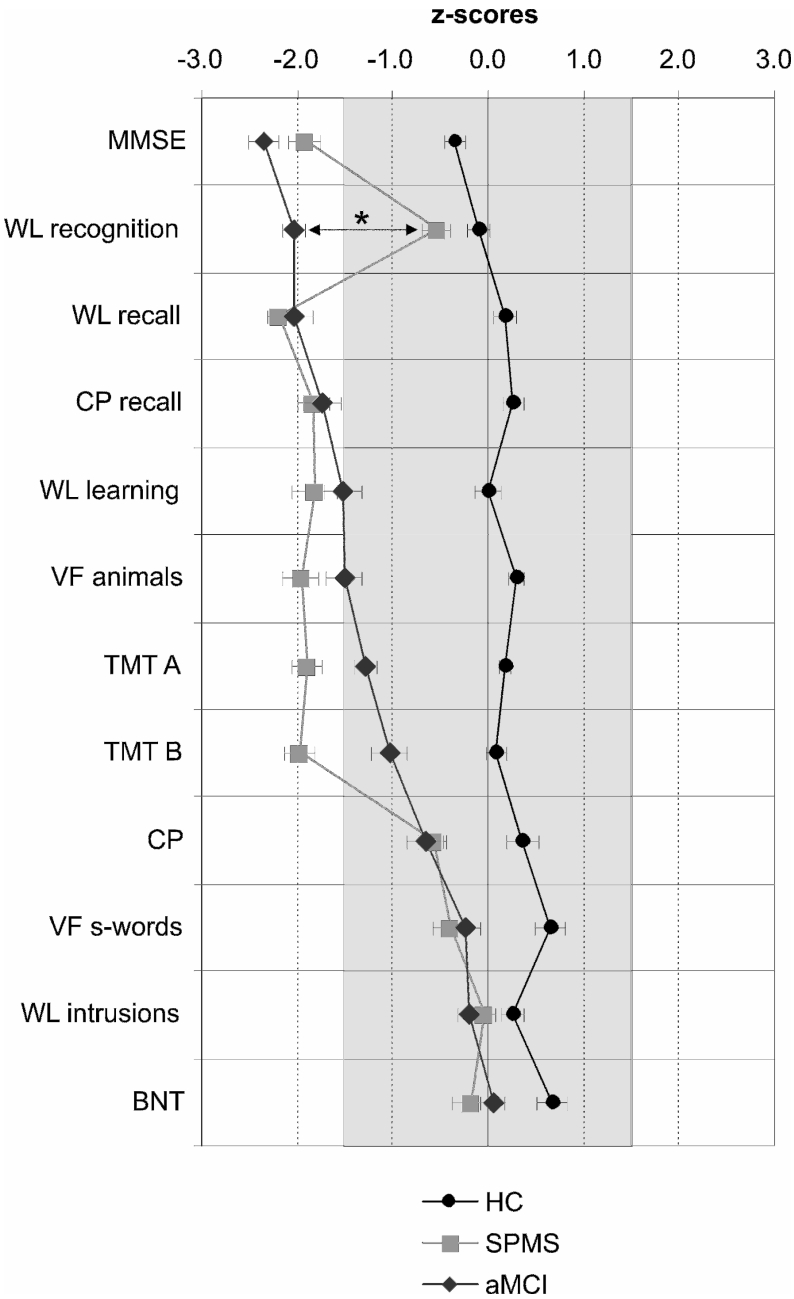

Figure 20. Comparisons of age-, education-, and gender-adjusted scores (z-scores) among healthy controls (HC), patients with secondary progressive multiple sclerosis (SPMS), and patients with amnestic mild cognitive impairment (aMCI) on the CERAD-plus test battery. WL: Word List; VF: Verbal Fluency; BNT: Boston Naming Test; CP: Constructional Praxis; TMT: Trail Making Test; MMSE: Mini Mental Status Examination. Means and standard errors of means are given. Higher z-scores reflect better performance. The area between the 7th and the 93rd percentile is shaded in grey. *Significant differences between patients with SPMS and aMCI at a Bonferroni-adjusted significance level of $p < .004$.

5.4 Discussion

To our knowledge, this is the first study to compare age-, education-, and gender-matched samples of elderly patients in the long-term course of SPMS and the prodromal phase of AD in order to find disease-dependent deterioration patterns, using the German version of the CERAD-plus test battery (Barth et al., 2005; Morris et al., 1989).

As hypothesized, and in contrast to what we observed in aMCI patients, recognition was preserved in SPMS patients. Recognition performance demonstrated at a z-score of -1.1 optimal sensitivity and specificity for discriminating SPMS and aMCI. Information processing speed and executive abilities were decreased in both patient groups as compared to the HC group. However, in contrast to patients with aMCI we found significant correlations between episodic memory recall (words and figures), information processing speed and executive abilities in SPMS patients. Thus, retrieval deficits in SPMS might be due to impairment of executive function and processing speed, whereas in aMCI a relationship between retrieval deficits and hippocampal atrophy is assumed (Dubois et al., 2007).

We did not detect an influence of demographic variables or affective state on cognitive performance in any group.

Executive function plays a critical role in memory retrieval (Gleichgerrcht et al., 2011) and is frequently affected in MS (Drew et al., 2009). Cortical atrophy due to grey matter loss, particularly in frontal structures (Ceccarelli et al., 2008; Kutzelnigg et al., 2005), possibly underlies the deterioration of executive abilities in long-term patients of the progressive MS subtypes (Zakzanis, 2000).

Although the pattern of deficits in verbal and figural episodic memory recall is similar in SPMS and aMCI, retrieval deficits predominate in SPMS, as indicated by severe impairment in verbal acquisition, delayed verbal recall, and delayed figural recall, with preservation of recognition (Chiaravalloti & DeLuca, 2008). Thus, memory impairment in SPMS reflects a deterioration of retrieval as information must be encoded adequately for successful recognition (Gleichgerrcht et al., 2011), and is related to impaired executive function (Drew et al., 2009; Zakzanis, 2000), possibly due to frontal degeneration (Ceccarelli et al., 2008; Kutzelnigg et al., 2005) and loss of information processing speed (Huijbregts et al., 2006). By contrast, aMCI patients exhibit all of these deficits as well as impaired recognition, pointing to impairment in encoding and storage as is typical of prodromal AD (Dubois et al., 2007). This episodic memory loss of the so-called hippocampal type (Dubois et al., 2010) is associated with neuronal loss in the medial temporal lobes in the early stages of the disease (Dubois et al., 2007).

Our findings emphasize that impaired learning and delayed recall are not necessarily evidence of an AD-related memory disorder, as episodic memory deficits appear in the long-term course of SPMS as well. However, SPMS-related deficits are associated with deterioration of information processing speed and executive function, but not impairment of memory storage.

In patients with SPMS, additional AD pathology must be considered if recall deficits are not mitigated during recognition testing. A reduced benefit from facilitated retrieval conditions at recall appears to be a reliable indicator of prodromal AD (Dubois et al., 2010). Therefore, memory impairment with no improvement under facilitated conditions in elderly patients with MS requires further examination.

However, there is evidence that vascular conditions in persons with MCI modulate the pattern of memory deficit (Villeneuve et al., 2011). Patients with MCI who do not exhibit concomitant vascular burden showed impairment of both free recall and recognition whereas patients with MCI revealed impaired free recall but intact recognition when vascular burden was high (Villeneuve et al., 2011). Hence, our proposed distinction between SPMS and aMCI on recognition testing may break down in aMCI patients with a high vascular load.

Furthermore, not all recognition tests might necessarily distinguish SPMS and aMCI patients. Recognition memory is widely viewed as consisting of two components: recollection (i.e. remembering specific contextual details about a prior learning episode) and familiarity (i.e. knowing that an item was presented, without having available any additional information about the learning episode) (Serra et al., 2010). It seems that patients with aMCI show relatively intact familiarity processing but impaired recollection (Serra et al., 2010). The CERAD-plus recognition task is assumed to be based on recollection (Squire et al., 2007). Therefore, particularly recognition tests which stress recollection distinguish SPMS and aMCI patients.

In conclusion, word list recognition tests that demands recollection process as used in the CERAD-plus test battery may permit to distinguish MS-related episodic memory impairment from AD-related deficits of encoding and storage and could help to identify AD-related pathology in SPMS patients.

5.5 Publication

Müller, S., Saur, R., Greve, B., Melms, A., Hautzinger, M., Fallgatter, A., and Leyhe, T. (2012). Recognition performance differentiates between elderly patients in the long term course of secondary progressive multiple sclerosis and amnestic mild cognitive impairment. *Multiple Sclerosis Journal*, accepted 19 August 2012.

6 General discussion

We investigated cognitive impairment in a large sample of well characterized elderly patients with RRMS, SPMS, aMCI and early AD with a focus on magnitude, pattern, and whether deficits are indicative of clinical course, subtype classification or differentiation between MS-related cognitive impairment and AD-related deficits.

The aim of the presented empirical work was to establish disease-dependent deterioration patterns in elderly patients with MS compared to patients with Alzheimer's disease pathology. The measures ranged from semi-structured interviews assessing autobiographical memory to further detailed and objective neuropsychological examination assessing a broad array of cognitive (mal)functions associated with AD (Dubois et al., 2010) that are also found in patients with MS (Chiaravalloti & DeLuca, 2008). This range of measures has not been reported before for this population and the scope of our studies therefore provides a baseline data for future investigations.

Our neuropsychological results differentiate between MS-related cognitive impairment and AD-related deficits and point at distinct disease mechanisms in different MS subtypes. Using the AMI (Kopelman et al., 1989) patients with SPMS exhibited a graded loss of personal incident memory akin to that seen in patients with early AD or aMCI patients whereas patients with RRMS were unaffected. AM retrieval deficits appear to coincide with consolidation disturbances related to functional impairment in the medial temporal lobe and hippocampus (Nadel & Moscovitch, 1997) whose integrity seem to be affected both in patients with aMCI or

AD (den Heijer et al., 2010; Leyhe et al., 2009) but also in SPMS, where the extend of hippocampal lesions depends on disease progression (Sicotte et al., 2008).

Using the German version of the CERAD test battery (Barth et al., 2005; Morris et al., 1989) we found substantial episodic memory deficits in the long-term course of SPMS. Our findings emphasize that impaired learning and delayed recall are not necessarily evidence of an Alzheimer's disease-related memory disorder. However, SPMS-related deficits are associated with deterioration of information processing speed and executive function, but not impairment of memory storage - the key early marker in prodromal stages of AD (Dubois et al., 2007).

Recent data suggest that certain mechanisms of neurodegeneration may be shared between MS and AD. Besides degeneration of neurons, axons, and synapses inflammation is also present in AD lesions, where it may have dual functions in amyloid clearance as well as in the propagation of neurodegeneration (Bjartmar & Trapp, 2001; Lassmann, 2011; Stadelmann, 2011; Trapp & Nave, 2008). Nevertheless, the relationships between biochemical surrogate markers of inflammation and neuronal damage, imaging findings and cognitive deficits are still unknown. Further studies are required to evaluate similarities and differences in the pathophysiology of MS and Alzheimer's disease. On the basis of possible correlations between clinical, imaging, and biochemical surrogate markers and the quality and quantity of neuropsychological deficits further hypotheses can be generated aiming at a better understanding of the underlying pathomechanisms of MS and Alzheimer's disease that may ultimately lead to new diagnostic and drug-therapeutic approaches.

7 References

Aebi, C. (2002). *Validierung der neuropsychologischen Testbatterie CERAD-NP: eine Multi-Center Studie*. Doctoral thesis. Universität Basel.

Albert, M. S., Dekosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 270–279.

Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *Journal of the International Neuropsychological Society, 7*(5), 631–639.

Alvarez, P., & Squire, L. R. (1994). Memory consolidation and the medial temporal lobe: a simple network model. *Proceedings of the National Academy of Sciences of the United States of America, 91*(15), 7041–7045.

Amato, M. P., Bartolozzi, M. L., Zipoli, V., Portaccio, E., Mortilla, M., Guidi, L., et al. (2004). Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. *Neurology, 63*(1), 89–93.

Amato, M. P., Zipoli, V., & Portaccio, E. (2006). Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies. *Journal of the Neurological Sciences, 245*(1-2), 41–46.

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders DSM-IV-TR* (4. ed.). Washington, DC: American Psychiatric Association Press.

Ascherio, A., & Munger, K. (2008). Epidemiology of multiple sclerosis: from risk factors to prevention. *Seminars in Neurology, 28*(1), 17–28.

Ascherio, A., & Munger, K. L. (2007). Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. *Annals of Neurology, 61*(6), 504–513.

Ascherio, A., & Munger, K. L. (2010). Epstein-barr virus infection and multiple sclerosis: a review. *Journal of Neuroimmune Pharmacology, 5*(3), 271–277.

Awad, A., & Stuve, O. (2010). Multiple sclerosis in the elderly patient. *Drugs & Aging, 27*(4), 283–294.

Backman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficit in Alzheimer's disease. *Brain, 124*(Pt 1), 96–102.

Baddeley, A. (2012). Working memory: theories, models, and controversies. *Annual Review of Psychology, 63*, 1–29.

Bakshi, R., Shaikh, Z. A., Miletich, R. S., Czarnecki, D., Dmochowski, J., Henschel, K., et al. (2000). Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Multiple Sclerosis, 6*(3), 181–185.

Barth, S., Schonknecht, P., Pantel, J., & Schroder, J. (2005). Neuropsychologische Profile in der Demenzdiagnostik: Eine Untersuchung mit der CERAD-NP-Testbatterie. *Fortschritte der Neurologie-Psychiatrie, 73*(10), 568–576.

Baudic, S., Barba, G. D., Thibaudet, M. C., Smagghe, A., Remy, P., & Traykov, L. (2006). Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Archives of Clinical Neuropsychology, 21*(1), 15–21.

Benedict, R. H. B., Fischer, J. S., Archibald, C. J., Arnett, P. A., Beatty, W. W., Bobholz, J., et al. (2002). Minimal neuropsychological assessment of MS patients: a consensus approach. *The Clinical Neuropsychologist, 16*(3), 381–397.

Benedict, R. H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society, 12*(4), 549–558.

Bergendal, G., Fredrikson, S., & Almkvist, O. (2007). Selective decline in information processing in subgroups of multiple sclerosis: an 8-year longitudinal study. *European Neurology, 57*(4), 193–202.

Bjartmar, C., & Trapp, B. D. (2001). Axonal and neuronal degeneration in multiple sclerosis: mechanisms and functional consequences. *Current Opinion in Neurology, 14*(3), 271–278.

Blennow, K., Leon, M. J. de, & Zetterberg, H. (2006). Alzheimer's disease. *Lancet, 368*(9533), 387–403.

Bobholz, J. A., Rao, S. M., Lobeck, L., Elsinger, C., Gleason, A., Kanz, J., et al. (2006). fMRI study of episodic memory in relapsing-remitting MS: correlation with T2 lesion volume. *Neurology, 67*(9), 1640–1645.

Bobholz, J., & Rao, S. (2003). Cognitive dysfunction in multiple sclerosis: a review of recent developments. *Current Opinion in Neurology, 16*(3), 283–288.

Bobinski, M., Leon, M. J. de, Convit, A., Santi, S. de, Wegiel, J., Tarshish, C. Y., et al. (1999). MRI of entorhinal cortex in mild Alzheimer's disease. *Lancet, 353*(9146), 38–40.

Bodling, A., Denney, D., & Lynch, S. (2009). Cognitive aging in patients with multiple sclerosis: a cross-sectional analysis of speeded processing. *Archives of Clinical Neuropsychology, 24*(8), 761–767.

Braak, E., Griffing, K., Arai, K., Bohl, J., Bratzke, H., & Braak, H. (1999). Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? *European Archives of Psychiatry and Clinical Neuroscience, 249 Suppl 3*, 14–22.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82*(4), 239–259.

Bruck, W., Lucchinetti, C., & Lassmann, H. (2002). The pathology of primary progressive multiple sclerosis. *Multiple Sclerosis, 8*(2), 93–97.

Buschke, H., Sliwinski, M. J., Kuslansky, G., & Lipton, R. B. (1997). Diagnosis of early dementia by the Double Memory Test: encoding specificity improves diagnostic sensitivity and specificity. *Neurology, 48*(4), 989–997.

Calabresi, P. A. (2004). Diagnosis and management of multiple sclerosis. *American Family Physician, 70*(10), 1935–1944.

Carlesimo, G. A., Perri, R., & Caltagirone, C. (2011). Category cued recall following controlled encoding as a neuropsychological tool in the diagnosis of Alzheimer's disease: a review of the evidence. *Neuropsychology Review, 21*(1), 54–65.

Ceccarelli, A., Rocca, M. A., Pagani, E., Colombo, B., Martinelli, V., Comi, G., & Filippi, M. (2008). A voxel-based morphometry study of grey matter loss in MS patients with different clinical phenotypes. *NeuroImage, 42*(1), 315–322.

Cerovski, B., Vidovic, T., Petricek, I., Popovic-Suic, S., Kordic, R., Bojic, L., et al. (2005). Multiple sclerosis and neuro-ophthalmologic manifestations. *Collegium Antropologicum, 29 Suppl 1*, 153–158.

Chen, T.-F., Chen, Y.-F., Cheng, T.-W., Hua, M.-S., Liu, H.-M., & Chiu, M.-J. (2009). Executive dysfunction and periventricular diffusion tensor changes in amnesic mild cognitive impairment and early Alzheimer's disease. *Human Brain Mapping, 30*(11), 3826–3836.

Chertkow, H., Whatmough, C., Saumier, D., & Duong, A. (2008). Cognitive neuroscience studies of semantic memory in Alzheimer's disease. *Progress in Brain Research, 169*, 393–407.

Chiaravalloti, N., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *Lancet Neurology, 7*(12), 1139–1151.

Cifelli, A., Arridge, M., Jezzard, P., Esiri, M. M., Palace, J., & Matthews, P. M. (2002). Thalamic neurodegeneration in multiple sclerosis. *Annals of Neurology, 52*(5), 650–653.

Collie, A., & Maruff, P. (2000). The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. *Neuroscience and Biobehavioral Reviews, 24*(3), 365–374.

Comi, G., Filippi, M., Martinelli, V., Campi, A., Rodegher, M., Alberoni, M., et al. (1995). Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. *Journal of the Neurological Sciences, 132*(2), 222–227.

Compston, A., & Coles, A. (2002). Multiple Sclerosis. *Lancet, 359*(9313), 1221–1231.

Compston, A., & Coles, A. (2008). Multiple Sclerosis. *Lancet, 372*(9648), 1502–1517.

Defer, G. L., Daniel, F., & Marie, R. M. (2006). [Study of episodic memory in multiple sclerosis using the California Verbal Learning Test: the data favour altered encoding]: Etude de la memoire episodique dans la sclerose en plaques grace au California Verbal Learning Test: donnees en faveur d'une alteration de l'encodage. *Revue Neurologique, 162*(8-9), 852–857.

DeLuca, J., Barbieri-Berger, S., & Johnson, S. K. (1994). The nature of memory impairments in multiple sclerosis: acquisition versus retrieval. *Journal of Clinical and Experimental Neuropsychology, 16*(2), 183–189.

DeLuca, J., Chelune, G. J., Tulsky, D. S., Lengenfelder, J., & Chiaravalloti, N. D. (2004). Is speed of processing or working memory the primary information processing deficit in multiple sclerosis? *Journal of Clinical and Experimental Neuropsychology, 26*(4), 550–562.

DeLuca, J., Gaudino, E. A., Diamond, B. J., Christodoulou, C., & Engel, R. A. (1998). Acquisition and storage deficits in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology, 20*(3), 376–390.

den Heijer. T., van der Lijn F, Koudstaal, P., Hofman, A., van, d., Krestin, G., et al. (2010). A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. *Brain, 133*(Pt 4), 1163–1172.

Denney, D., Lynch, S., Parmenter, B., & Horne, N. (2004). Cognitive impairment in relapsing and primary progressive multiple sclerosis: mostly a matter of speed. *Journal of the International Neuropsychological Society, 10*(7), 948–956.

Denney, La Sworowski, & Lynch, S. G. (2005). Cognitive impairment in three subtypes of multiple sclerosis. *Archive of Clinical Neuropsychology, 20*(8), 967–981.

Desgranges, B., Baron, J.-C., Lalevee, C., Giffard, B., Viader, F., La Sayette, V. de, & Eustache, F. (2002). The neural substrates of episodic memory impairment in Alzheimer's disease as revealed by FDG-PET: relationship to degree of deterioration. *Brain, 125*(Pt 5), 1116–1124.

Di Pauli, F., Reindl, M., Ehling, R., Schautzer, F., Gneiss, C., Lutterotti, A., et al. (2008). Smoking is a risk factor for early conversion to clinically definite multiple sclerosis. *Multiple Sclerosis, 14*(8), 1026–1030.

Drew, M., Starkey, N., & Isler, R. (2009). Examining the link between information processing speed and executive functioning in multiple sclerosis. *Archives of Clinical Neuropsychology, 24*(1), 47–58.

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., Dekosky, S. T., Barberger-Gateau, P., et al. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurology, 9*(11), 1118–1127.

Dubois, B., Feldman, H., Jacova, C., Dekosky, S., Barberger-Gateau, P., Cummings, J., et al. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurology, 6*(8), 734–746.

Duque, B., Sepulcre, J., Bejarano, B., Samaranch, L., Pastor, P., & Villoslada, P. (2008). Memory decline evolves independently of disease activity in MS. *Multiple Sclerosis, 14*(7), 947–953.

Ferri, C. P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., et al. (2005). Global prevalence of dementia: a Delphi consensus study. *Lancet, 366*(9503), 2112–2117.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189–198.

Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C. A., Kartsounis, L. D., Thompson, A. J., et al. (1997). Executive function in multiple sclerosis. The role of frontal lobe pathology. *Brain, 120 (Pt 1)*, 15–26.

Fox, R. J., & Cohen, J. A. (2001). Multiple sclerosis: the importance of early recognition and treatment. *Cleveland Clinic Journal of Medicine, 68*(2), 157–171.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R., Ritchie, K., Broich, K., et al. (2006). Mild cognitive impairment. *Lancet, 367*(9518), 1262–1270.

Geurts, J. J., Bo, L., Roosendaal, S. D., Hazes, T., Daniels, R., Barkhof, F., et al. (2007). Extensive hippocampal demyelination in multiple sclerosis. *Journal of Neuropathology & Experimental Neurology, 66*(9), 819–827.

Giovannoni, G., & Ebers, G. (2007). Multiple sclerosis: the environment and causation. *Current Opinion in Neurology, 20*(3), 261–268.

Gleichgerrcht, E., Torralva, T., Martinez, D., Roca, M., & Manes, F. (2011). Impact of executive dysfunction on verbal memory performance in patients with Alzheimer's disease. *Journal of Alzheimer's Disease, 23*(1), 79–85.

Gourraud, P.-A., Harbo, H. F., Hauser, S. L., & Baranzini, S. E. (2012). The genetics of multiple sclerosis: an up-to-date review. *Immunological Reviews, 248*(1), 87–103.

Grober, E., Sanders, A. E., Hall, C., & Lipton, R. B. (2010). Free and cued selective reminding identifies very mild dementia in primary care. *Alzheimer Disease and Associated Disorders, 24*(3), 284–290.

Guerin, F., Belleville, S., & Ska, B. (2002). Characterization of visuoconstructional disabilities in patients with probable dementia of Alzheimer's type. *Journal of Clinical and Experimental Neuropsychology, 24*(1), 1–17.

Haensch, C.-A., & Jorg, J. (2006). Autonomic dysfunction in multiple sclerosis. *Journal of Neurology, 253 Suppl 1*, I3-9.

Hampel, H., Prvulovic, D., Teipel, S., Jessen, F., Luckhaus, C., Frolich, L., et al. (2011). The future of Alzheimer's disease: the next 10 years. *Progress in Neurobiology, 95*(4), 718–728.

Hardy, J. (2006). Has the amyloid cascade hypothesis for Alzheimer's disease been proved? *Current Alzheimer Research, 3*(1), 71–73.

Haussleiter, I. S., Brune, M., & Juckel, G. (2009). Psychopathology in multiple sclerosis: diagnosis, prevalence and treatment. *Therapeutic Advances in Neurological Disorders, 2*(1), 13–29.

Hautzinger, M., Keller F, & Kühner C (2007). *Beck Depressionsinventar II. Testhandbuch.* Frankfurt a.M.: Pearson.

Hein, T., & Hopfenmuller, W. (2000). Projection of the number of multiple sclerosis patients in Germany [Hochrechnung der Zahl an Multiple Sklerose erkrankten Patienten in Deutschland]. *Der Nervenarzt, 71*(4), 288–294.

Huijbregts, S. C., Kalkers, N. F., Sonneville, L. M. de, Groot, V. de, & Polman, C. H. (2006). Cognitive impairment and decline in different MS subtypes. *Journal of the Neurological Sciences, 245*(1-2), 187–194.

Janculjak, D., Mubrin, Z., Brinar, V., & Spilich, G. (2002). Changes of attention and memory in a group of patients with multiple sclerosis. *Clinical Neurology & Neurosurgery, 104*(3), 221–227.

Kenealy, P., Beaumont, J., Lintern, T., & Murrell, R. (2002). Autobiographical memory in advanced multiple sclerosis: assessment of episodic and personal semantic memory across three time spans. *Journal of the International Neuropsychological Society, 8*(6), 855–860.

Kopelman, M. D., Wilson, B. A., & Baddeley, A. D. (1989). The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *Journal of Clinical and Experimental Neuropsychology, 11*(5), 724–744.

Kopelman, M., Bright, P., Fulker, H., Hinton, N., Morrison, A., & Verfaellie, M. (2009). Remote semantic memory in patients with Korsakoff's syndrome and herpes encephalitis. *Neuropsychology, 23*(2), 144–157.

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology, 33*(11), 1444–1452.

Kutzelnigg, A., Lucchinetti, C. F., Stadelmann, C., Bruck, W., Rauschka, H., Bergmann, M., et al. (2005). Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain, 128*(Pt 11), 2705–2712.

Kwak, Y. T. (2004). "Closing-in" phenomenon in Alzheimer's disease and subcortical vascular dementia. *BioMedCentral Neurology, 4*, 3.

Lassmann, H. (2011). Mechanisms of neurodegeneration shared between multiple sclerosis and Alzheimer's disease. *Journal of Neural Transmission, 118*(5), 747–752.

Lengenfelder, J., Bryant, D., Diamond, B. J., Kalmar, J. H., Moore, N. B., & DeLuca, J. (2006). Processing speed interacts with working memory efficiency in multiple sclerosis. *Archive of Clinical Neuropsychology, 21*(3), 229–238.

Leyhe, T., Laske, C., Buchkremer, G., Wormstall, H., & Wiendl, H. (2005). Demenz als Erstsymptom bei spät beginnender Multipler Sklerose. Fallserie mit Literaturubersicht. *Der Nervenarzt, 76*(6), 748–755.

Leyhe, T., Müller, S., Eschweiler, G. W., & Saur, R. (2010). Deterioration of the memory for historic events in patients with mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia, 48*(14), 4093–4101.

Leyhe, T., Müller, S., Milian, M., Eschweiler, G., & Saur, R. (2009). Impairment of episodic and semantic autobiographical memory in patients with mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia, 47*(12), 2464–2469.

Lublin, F. D., & Reingold, S. C. (1996). Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology, 46*(4), 907–911.

McCarthy, M., Beaumont, J. G., Thompson, R., & Peacock, S. (2005). Modality-specific aspects of sustained and divided attentional performance in multiple sclerosis. *Archive of Clinical Neuropsychology, 20*(6), 705–718.

McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H. P., Lublin, F. D., et al. (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology, 50*(1), 121–127.

McGeer, P. L., & McGeer, E. G. (2001). Inflammation, autotoxicity and Alzheimer disease. *Neurobiology of Aging, 22*(6), 799–809.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*(7), 939–944.

Meeter, M., Eijsackers, E. V., & Mulder, J. L. (2006). Retrograde amnesia for autobiographical memories and public events in mild and moderate Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology, 28*(6), 914–927.

Memory Clinic Basel (2005). *CERAD-Plus: The Consortium to Establish a Registry for Alzheimer's Disease.* Basel Universitätsspital.

Metzler-Baddeley, C. (2007). A review of cognitive impairments in dementia with Lewy bodies relative to Alzheimer's disease and Parkinson's disease with dementia. *Cortex, 43*(5), 583–600.

Meulenbroek, O., Rijpkema, M., Kessels, R., Rikkert, M., & Fernandez, G. (2010). Autobiographical memory retrieval in patients with Alzheimer's disease. *NeuroImage, 53*(1), 331–340.

Milo, R., & Kahana, E. (2010). Multiple sclerosis: geoepidemiology, genetics and the environment. *Autoimmunity Reviews, 9*(5), A387-94.

Minagar, A., Toledo, E. G., Alexander, J. S., & Kelley, R. E. (2004). Pathogenesis of brain and spinal cord atrophy in multiple sclerosis. *Journal of Neuroimaging, 14*(3 Suppl), 5S-10S.

Minden, S. L., Frankel, D., Hadden, L. S., Srinath, K. P., & Perloff, J. N. (2004). Disability in elderly people with multiple sclerosis: An analysis of baseline data from the Sonya Slifka Longitudinal Multiple Sclerosis Study. *NeuroRehabilitation, 19*(1), 55–67.

Moller, H. J., & Graeber, M. B. (1998). The case described by Alois Alzheimer in 1911. Historical and conceptual perspectives based on the clinical record and neurohistological sections. *European Archives of Psychiatry and Clinical Neuroscience, 248*(3), 111–122.

Morgen, K., Sammer, G., Courtney, S. M., Wolters, T., Melchior, H., Blecker, C. R., et al. (2006). Evidence for a direct association between cortical atrophy and cognitive impairment in relapsing-remitting MS. *NeuroImage, 30*(3), 891–898.

Morris, J. C., Heyman, A., Mohs, R. C., Hughes, J. P., van Belle, G., Fillenbaum, G., et al. (1989). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology, 39*(9), 1159–1165.

Murray, T. J. (2009). The history of multiple sclerosis: the changing frame of the disease over the centuries. *Journal of the Neurological Sciences, 277 Suppl 1*, S3-8.

Nadel, L., & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinion in Neurobiology, 7*(2), 217–227.

Nagy, H., Bencsik, K., Rajda, C., Benedek, K., Beniczky, S., Keri, S., & Vecsei, L. (2006). The effects of reward and punishment contingencies on decision-making in multiple sclerosis. *Journal of the International Neuropsychological Society, 12*(4), 559–565.

Nelson, P. T., Braak, H., & Markesbery, W. R. (2009). Neuropathology and cognitive impairment in Alzheimer disease: a complex but coherent relationship. *Journal of Neuropathology and Experimental Neurology, 68*(1), 1–14.

Ness, J. M., Chabas, D., Sadovnick, A. D., Pohl, D., Banwell, B., & Weinstock-Guttman, B. (2007). Clinical features of children and adolescents with multiple sclerosis. *Neurology, 68*(16 Suppl 2), S37-45.

Nessler, S., & Bruck, W. (2010). Advances in multiple sclerosis research in 2009. *Journal of Neurology, 257*(9), 1590–1593.

Nestor, P. J., Fryer, T. D., & Hodges, J. R. (2006). Declarative memory impairments in Alzheimer's disease and semantic dementia. *NeuroImage, 30*(3), 1010–1020.

Nestor, P. J., Graham, K. S., Bozeat, S., Simons, J. S., & Hodges, J. R. (2002). Memory consolidation and the hippocampus: further evidence from studies of autobiographical memory in semantic dementia and frontal variant frontotemporal dementia. *Neuropsychologia, 40*(6), 633–654.

Noseworthy, J. H., Lucchinetti, C., Rodriguez, M., & Weinshenker, B. G. (2000). Multiple sclerosis. *The New England Journal of Medicine, 343*(13), 938–952.

Nylander, A., & Hafler, D. A. (2012). Multiple Sclerosis. *The Journal of Clinical Investigation, 122*(4), 1180–1188.

Olivares, T., Nieto, A., Sanchez, M. P., Wollmann, T., Hernandez, M. A., & Barroso, J. (2005). Pattern of neuropsychological impairment in the early phase of relapsing-remitting multiple sclerosis. *Multiple Sclerosis, 11*(2), 191–197.

Pagani, E., Rocca, M., Gallo, A., Rovaris, M., Martinelli, V., Comi, G., & Filippi, M. (2005). Regional brain atrophy evolves differently in patients with multiple sclerosis according to clinical phenotype. *American Journal of Neuroradiology, 26*(2), 341–346.

Parmenter, B., Shucard, J., & Shucard, D. (2007). Information processing deficits in multiple sclerosis: a matter of complexity. *Journal of the International Neuropsychological Society, 13*(3), 417–423.

Paul, R. H., Blanco, C. R., Hames, K. A., & Beatty, W. W. (1997). Autobiographical memory in multiple sclerosis. *Journal of the International Neuropsychological Society, 3*(3), 246–251.

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. *Brain, 122 (Pt 3)*, 383–404.

Perry, R. J., Watson, P., & Hodges, J. R. (2000). The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. *Neuropsychologia, 38*(3), 252–271.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine, 256*(3), 183–194.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., et al. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology, 58*(12), 1985–1992.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology, 56*(3), 303–308.

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., et al. (2011). Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology, 69*(2), 292–302.

Polman, C. H., Reingold, S. C., Edan, G., Filippi, M., Hartung, H. P., Kappos, L., et al. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Annals of Neurology, 58*(6), 840–846.

Pugliatti, M., Rosati, G., Carton, H., Riise, T., Drulovic, J., Vecsei, L., & Milanov, I. (2006). The epidemiology of multiple sclerosis in Europe. *European Journal of Neurology, 13*(7), 700–722.

Qiu, W., Wu, J.-S., Castley, A., James, I., Joseph, J., Christiansen, F. T., et al. (2010). Clinical profile and HLA-DRB1 genotype of late onset multiple sclerosis in Western Australia. *Journal of Clinical Neuroscience, 17*(8), 1009–1013.

Rao, S. M., Leo, G. J., & St Aubin-Faubert, P. (1989). On the nature of memory disturbance in multiple sclerosis. *Journal of Clinical and Experimental neuropsychology, 11*(5), 699–712.

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology, 41*(5), 685–691.

Reitan, R. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Percepual &t Motor Skills, 8*(3), 271–276.

Rendell, P. G., Jensen, F., & Henry, J. D. (2007). Prospective memory in multiple sclerosis. *Journal of the International Neuropsychological Society, 13*(3), 410–416.

Ribot, T. (1881). *Les maladies de la mémoire.* Paris: Baillière.

Riccitelli, G., Rocca, M., Pagani, E., Rodegher, M., Rossi, P., Falini, A., et al. (2011). Cognitive impairment in multiple sclerosis is associated to different patterns of gray matter atrophy according to clinical phenotype. *Human Brain Mapping, 32*(10), 1535–1543.

Roosendaal, S., Bendfeldt, K., Vrenken, H., Polman, C., Borgwardt, S., Radue, E., et al. (2011). Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability. *Multiple Sclerosis, 17*(9), 1098–1106.

Rovaris, M., Judica, E., Gallo, A., Benedetti, B., Sormani, M. P., Caputo, D., et al. (2006). Grey matter damage predicts the evolution of primary progressive multiple sclerosis at 5 years. *Brain, 129*(Pt 10), 2628–2634.

Sailer, M., Fischl, B., Salat, D., Tempelmann, C., Schonfeld, M. A., Busa, E., et al. (2003). Focal thinning of the cerebral cortex in multiple sclerosis. *Brain, 126*(Pt 8), 1734–1744.

Salmon, D. P., & Bondi, M. W. (2009). Neuropsychological assessment of dementia. *Annual Review of Psychology, 60*, 257–282.

Salmon, E., Lekeu, F., Bastin, C., Garraux, G., & Collette, F. (2008). Functional imaging of cognition in Alzheimer's disease using positron emission tomography. *Neuropsychologia, 46*(6), 1613–1623.

Serra, L., Bozzali, M., Cercignani, M., Perri, R., Fadda, L., Caltagirone, C., & Carlesimo, G. A. (2010). Recollection and familiarity in amnesic mild cognitive impairment. *Neuropsychology, 24*(3), 316–326.

Sicotte, N. L., Kern, K. C., Giesser, B. S., Arshanapalli, A., Schultz, A., Montag, M., et al. (2008). Regional hippocampal atrophy in multiple sclerosis. *Brain, 131*(Pt 4), 1134–1141.

Simon, K. C., Munger, K. L., & Ascherio, A. (2012). Vitamin D and multiple sclerosis: epidemiology, immunology, and genetics. *Current Opinion in Neurology, 25*(3), 246–251.

Smestad, C., Sandvik, L., Landro, N. I., & Celius, E. G. (2010). Cognitive impairment after three decades of multiple sclerosis. *European Journal of Neurology, 17*(3), 499–505.

Smith, M. Z., Esiri, M. M., Barnetson, L., King, E., & Nagy, Z. (2001). Constructional apraxia in Alzheimer's disease: association with occipital lobe pathology and accelerated cognitive decline. *Dementia and Geriatric Cognitive Disorders, 12*(4), 281–288.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 280–292.

Squire, L. (2004). Memory systems of the brain: a brief history and current perspective. *Neurobiology of Learning and Memory, 82*(3), 171–177.

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. *Current Opinion in Neurobiology, 5*(2), 169–177.

Squire, L. R., Wixted, J. T., & Clark, R. E. (2007). Recognition memory and the medial temporal lobe: a new perspective. *Nature Reviews, 8*(11), 872–883.

Stadelmann, C. (2011). Multiple sclerosis as a neurodegenerative disease: pathology, mechanisms and therapeutic implications. *Current Opinion in Neurology, 24*(3), 224–229.

Stadelmann, C., Albert, M., Wegner, C., & Bruck, W. (2008). Cortical pathology in multiple sclerosis. *Current Oopinion in Neurology, 21*(3), 229–234.

Svoboda, E., McKinnon, M., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia, 44*(12), 2189–2208.

Thornton, A. E., Raz, N., & Tucke, K. A. (2002). Memory in multiple sclerosis: contextual encoding deficits. *Journal of the International Neuropsychological Society, 8*(3), 395–409.

Thurstone, L. L. (1938). *Primary mental abilities.* Chicago: University of Chicago Press.

Trapp, B., & Nave, K.-A. (2008). Multiple sclerosis: an immune or neurodegenerative disorder? *Annual Review of Neuroscience, 31*, 247–269.

Tulving, E. (2002). Episodic memory: from mind to brain. *Annual Review of Psychology, 53*, 1–25.

Twamley, E. W., Ropacki, S. A. L., & Bondi, M. W. (2006). Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society, 12*(5), 707–735.

Vemuri, P., & Jack, C. R., JR (2010). Role of structural MRI in Alzheimer's disease. *Alzheimer's Research & Therapy, 2*(4), 23.

Villeneuve, S., Massoud, F., Bocti, C., Gauthier, S., & Belleville, S. (2011). The nature of episodic memory deficits in MCI with and without vascular burden. *Neuropsychologia, 49*(11), 3027–3035.

Wachowius, U., Talley, M., Silver, N., Heinze, H. J., & Sailer, M. (2005). Cognitive impairment in primary and secondary progressive multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology, 27*(1), 65–77.

Whitwell, J. L., Shiung, M. M., Przybelski, S. A., Weigand, S. D., Knopman, D. S., Boeve, B. F., et al. (2008). MRI patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. *Neurology, 70*(7), 512–520.

Whitwell, J., Przybelski, S., Weigand, S., Knopman, D., Boeve, B., Petersen, R., & Jack, C. (2007). 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain, 130*(Pt 7), 1777–1786.

World Health Organisation (1993). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines* (Reprinted.). Geneva: World Health Organisation.

Wylezinska, M., Cifelli, A., Jezzard, P., Palace, J., Alecci, M., & Matthews, P. M. (2003). Thalamic neurodegeneration in relapsing-remitting multiple sclerosis. *Neurology, 60*(12), 1949–1954.

Xu, Y., Jack, C. R., JR, O'Brien, P. C., Kokmen, E., Smith, G. E., Ivnik, R. J., et al. (2000). Usefulness of MRI measures of entorhinal cortex versus hippocampus in AD. *Neurology, 54*(9), 1760–1767.

Zakzanis, K. K. (2000). Distinct neurocognitive profiles in multiple sclerosis subtypes. *Archives of Clinical Neuropsychology, 15*(2), 115–136.

Ziegler, U., & Doblhammer, G. (2009). Prevalence and incidence of dementia in Germany-a study based on data from the public sick funds in 2002 [Pravalenz und Inzidenz von Demenz in Deutschland-Eine Studie auf Basis von Daten der gesetzlichen Krankenversicherungen von 2002]. *Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)), 71*(5), 281–290.

Zivadinov, R., Sepcic, J., Nasuelli, D., Masi, R. de, Bragadin, L. M., Tommasi, M. A., et al. (2001). A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 70*(6), 773–780.