COGNITIVE DYSFUNCTION IN A POPULATION-BASED SAMPLE OF MULTIPLE SCLEROSIS PATIENTS

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1998

Acknowledgements

This study was started on the initiative of Per Soelberg Sørensen, who I want to thank for his support throughout the study. Many thanks to Karen Schreiber, for your close collaboration, your tremendous effort managing the study population, and for all you have taught me about neurology during the study. I also thank you for your indispensable linguistic support. Many thanks to my first tutor Anders Gade for your generous inspiration in my work, both during this study and during my time as a student in psychology. Special thanks to my second tutor Gunilla Öberg for everything you have taught me about clinical neuropsychology, and for your always inspiring and enthusiastic attitude. I am also extremely grateful to my third tutor Erik Lykke Mortensen for guiding me through the troublesome statistical galaxies. Thanks a lot to Morten Blinkenberg, and my fellow colleagues Karin Nørgaard, Irene Mortensen, and Lisbet Marstrand for your help and support during the project. I also want to thank the staff at the MS clinic, and my fellow colleagues at the Department of Neurology, Rigshospitalet for the warm and inspiring collaboration. Lastly, I would like to express my great appreciation to my wife, children, and family for your patient support of my work through these years. Hopefully, they will also bear me in the future.

Copenhagen, October 1998
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1. INTRODUCTION

Multiple sclerosis (MS) is the most common neurological illness among young adults. The disease produces widespread lesions in white matter of the central nervous system. The influential French neurologist, Jean-Martin Charcot, is credited with initially describing the symptoms of MS and naming the disease. In his famous Salpetrière lectures in 1877 [31], he described the physical symptoms, but especially emphasised the neurobehavioral problems. Despite that, the neurobehavioral aspects of MS were almost neglected until 10-15 years ago [137,145]. The general assumption among clinicians and scientists was that cognitive dysfunction only occurred in a small number of MS patients and only late in the course of the disease. However, during the last 10 years a number of neuropsychological studies have accumulated evidence that cognitive dysfunction is more prevalent than previously assumed. Furthermore, it is now well established that dementia can occur much earlier in the course of the disease than previously described.

Despite the high activity in this area of research during the last 10 years there are still many questions to be answered. Techniques for visualising the brain have improved dramatically within the last ten years, and especially magnetic resonance imaging (MRI) plays an important role in MS research. It is now possible to follow different aspects of the pathologic process in vivo. However, the associations between the amount of lesioned brain tissue on MRI and physical symptoms and cognitive symptoms are often only modest. The reasons for this weak correlation between cognitive impairment and other measures of disease severity are still poorly understood, and much work has to be done to understand this complex relationship between brain structure and behaviour better.

The pathology in MS affects sites throughout the CNS in random patterns, resulting in a highly variable presentation of symptoms in time and space. This heterogeneity first of all makes it difficult to form homogeneous subgroups of patients, allowing inter- and

intraindividual comparisons, within and between studies. In relation to neuropsychological testing the heterogeneity further increases the problems with variability, inherent in all

neuropsychological research. This is one of the reasons for the limited knowledge of the true prevalence of cognitive dysfunction in MS.

Another reason for the minimal focus on dementia in MS may be more sociological in origin. MS societies and other organisations dealing with MS might not be interested in promoting MS as an illness which frequently leads to dementia. This image might be seen as a cause for difficulties in getting new members and money. However, cognitive impairment is a very disabling condition, affecting all aspects of the patients lives. Deficits in cognitive function, for example memory and attentional dysfunction, are often difficult to compensate effectively for. The effect of a paralysed leg can be effectively relieved by a wheelchair, while for example dysfunction in focused attention may cause severe limitations in the patients' interaction with others. Furthermore, it is not unusual to hear MS patients claim that they feel ashamed of their cognitive difficulties.

It therefore seems reasonable to pay more attention to cognitive impairment in MS. Although neurologists today are more familiar with the high prevalence of cognitive dysfunction than previously, these symptoms still tend to be overlooked in standard neurological examinations [20]. One might suspect cognitive symptoms to be even more overlooked among general practitioners.

This thesis focuses on the prevalence and pattern of cognitive dysfunction in MS. A general description of the background is presented in the first part. The second part offers a comprehensive review of the literature on cognitive function in MS. In the third part a study of a randomly selected population of MS patients is presented. The study population, drawn from the Danish Multiple Sclerosis Registry (DMSR) is a random stratified selection of 99 MS patients between 35 and 50 years of age.

The main objectives of the study were to examine:

- ***The prevalence of cognitive dysfunction in MS in a random sample of MS patients between 35 and 50 years of age.***
- ***The pattern of cognitive dysfunction in this group of MS patients***
- ***The association between cognitive dysfunction and measures of neurological disability and disease variables.***

2. MULTIPLE SCLEROSIS

2.1. Pathology and aetiology

Multiple Sclerosis (MS) is a disease exclusively of the central nervous system, where loss of myelin in white matter is the predominant manifestation. The precise pathophysiology of MS is still not known, but some histological characteristics have been described[107,152]: Initially there is a breakdown of the blood brain barrier (it is still unclear what makes the barrier open and how) and an inflammation (often perivascular) takes place. The neuropathological process of MS often leaves the axons relatively intact. Therefore the cessation of neural transmission is often not complete. Remyelination of axons occurs to some extent, both in acute and chronic plaques, but this process is not yet fully understood. The disease causes numerous lesions which are typically circumscribed and in general macroscopically visible. The lesions are called plaques and vary greatly in size (from millimetres to several centimetres) and distribution.

In an autopsy study by Brownell & Hughes [29] the total number of plaques was counted in 22 MS patients (mean 72 plaques/patient). The majority of plaques (74%) involved the white matter, 17% were situated in the junction of cortex and white matter, and 9% were located entirely within the cortex or central grey matter. However, there was a high concentration of plaques around the ventricles. 40 % of the plaques were located in the periventricular white matter, while 50% were situated within one of the major lobes. 22% of the cerebral plaques were situated in the frontal lobes, 15% in the parietal lobes, 12% in the temporal lobes and 1 % in the occipital lobes.

The aetiology of MS is not yet known, although many efforts are invested in the research. The illness seems to depend on a complex interaction between environmental factors and genetics. Studies on twins indicate a genetic factor in the development of the disease. The concordance of MS in monozygotic twins is approximately 30 % and about 5% in dizygotes and siblings. Close relatives have a 10-15 times increased risk for MS. However, this can not fully explain the development of MS, and in the search for environmental factors on a number of infectious agents have been suggested - for example measles, rubella, influenza, and canine distemper virus in dogs [36]. A small number of studies indicated that people less than 15 years of age at

the time of migration from low risk to high risk areas take on the risk in their new country, indicating an influence of environmental factors [94]. The puzzle of the aetiology is still unsolved, but today evidence indicates a combination of genetic disposition and some kind of environmental exposure.

2.2. Epidemiology

Almost twice as many women as men acquire the illness with ratios varying between 1:1.5 and 1:2 [169] The average age for the clinical onset is 30 years and most patients with MS fall into the age group 15-50 years. However, in a small minority of patients there is a very late onset after the age of 59 [8]. The prevalence of MS across the world is quite variable - between 5 and 110/100.000 [94]. In Denmark the prevalence is approximately 60/100.000 [86]. However, the prevalence is not always the best direct measure of disease frequency, because it is affected by a combination of several factors such as the incidence rate, the mean duration of the disease, and the mortality [86]. The incidence may be considered a more direct measure of the frequency of MS. Studies on the incidence of MS show diverging results - between 1 and 6/100.000 (mean approximately 4/100.000) [84,85,140]. It is not clear whether the incidence of multiple sclerosis is increasing, decreasing or stable. Studies have reached all three conclusions, and this might simply be caused by differences in diagnostic methods and technology, or the general awareness of MS among practitioners [110]. It is a general belief that the frequency of MS increases with increasing latitude (the so-called north-south gradient), but this relationship turns out not to be that simple[34]. Koch-Henriksen [84] reported significant fluctuations in incidence rates over time in Scandinavia and Finland. Furthermore the incidence appeared to be lowest in some of the northernmost regions, indicating that the north-south gradient for risk of MS does not hold true for high latitudes. It might therefore be more appropriate to subdivide the world into zones of high prevalence (about 45/100.000), medium prevalence (about 15/100.000), and low prevalence (under 5/100.000)[94].

2.3. Diagnosis and course

It is often difficult to diagnose MS and there is no single specific laboratory test for the illness. The diagnosis is generally based on clinical and/or paraclinical evidence for dissemination of white matter lesions in time and space. There are a number of ways to get this information.

First of all a careful history and a neurologic examination have to be done. Using this information from the patient or relatives, it is often possible for the neurologist to map the initial symptoms and course of the disease. The real onset of MS is sometimes years before the patient came to medical attention and had MS diagnosed. As long as paraclinical tests are not able to give the definitive diagnosis, the classical neurological examination still plays a major role. The specific pattern of neurological symptoms mirrors lesion sites quite precisely, and the examination is often able to document dissemination of lesions in space. Some of the typical symptoms at presentation are optic neuritis (about 20%), motor symptoms (about 20%), sensory symptoms (about 40%), diplopia (about 10%), and ataxia (about 15%) [83,190].

Today a number of paraclinical tests play an important role in the diagnostic procedure. Using lumbar puncture a small amount of the cerebrospinal fluid (CSF) is taken for laboratory analysis. The measurement of oligoclonal IgG bands in CSF is one of the most valuable tests performed routinely in the diagnosis of MS, and strongly supportive of MS[4]. A number of other abnormal CSF variables are also frequently found in patients with definite MS - abnormal blood/CSF barrier function, increased IgG quotient and increased cell count.

The measurement of evoked potentials provides important information about the velocity of central nerve conduction. Demyelinated axons cannot conduct in a rapid normal manner, even without neurologic symptoms. Traditional neurophysiological measures of visual evoked potentials (VEP), auditory evoked potentials (AEP), somatosensory evoked potentials (SSEP), and motor evoked potentials (MEP) are used in diagnosing MS. Ravnborg et al. [148] evaluated the methods and found VEP positive in 67% of the MS patients, AEP in 42%, SSEP in 63%, and MEP in 83%. The information gained by MRI was best supplemented by VEP, and MEP was in closest agreement with MRI (concordance 85%).

The most sensitive method for visualising MS lesions is Magnetic Resonance Imaging (MRI). This method gives in vivo visual evidence of dissemination of lesions in space. MRI plays a very central role in MS research and is described in greater detail in section 2.4.

A diagnosis of MS is often made according to some specific criteria. The first widely used criteria were the Schumacher criteria [164] from 1965. The medical history or the neurological examination should reveal evidence for two or more lesions in the CNS, the onset should be between age 10 and 50, the symptoms and signs should reflect primarily white matter involvement, and there should be no better explanation for the symptoms. Eighteen years later the need for incorporating supportive laboratory data into the diagnostic criteria resulted in new guidelines for the MS diagnosis - the Poser criteria [132]. The Poser criteria include four kinds of evidence for MS: 1) attacks (bouts of neurological symptoms and signs lasting more than 24 hours), 2) clinical evidence, 3) paraclinical evidence (e.g. VEP, SSEP, AEP, MRI), and 4) evidence from CSF (oligoclonal bands (OB) and IgG-index). Various combinations of these distinct forms of evidence are grouped in four categories according to the probability of MS (table 2.1).

Table 2.1. The Poser Criteria

	Category	Attacks	Clinical evidence		Paraclinical evidence	CSF OB/IgG
A.	**Clinically definite MS**					
	CDMS A1	2	2			
	CDMS A2	2	1	and	1	
B.	**Laboratory supported definite MS**					
	LSDMS B1	2	1	or	1	+
	LSDMS B2	1	2			+
	LSDMS B3	1	1	and	1	+
C.	**Clinically probable MS**					
	CPMS C1	2	1			
	CPMS C2	1	2			
	CPMS C3	1	1	and	1	
D.	**Laboratory supported probable MS**					
	LSPMS D1	2				+

The numbers in this table refer to the number of attacks, clinical evidence and/or paraclinical evidence in the different combinations defining the four types of MS diagnosis. Combinations marked with "+" indicate that positive evidence from CSF need to be present.

It is still impossible to predict the course of the disease. There is an enormous variability in the course of MS, going from patients with multiple attacks, leading to death within a year, to patients with one or two exacerbations in a lifetime. However, there seems to be some crude pattern in the course of MS. On a group level fast progressive MS is related to patients with high numbers of attacks and shorter first interattack interval[191]. Controversy exists about the

most appropriate way of defining the clinical course of MS. There is no clear common criteria among clinicians for the terms used to describe forms or clinical stages of the illness [100]. The categories often used in the literature are:

1. **Relapsing/remitting (RR):** A pattern of relapses with new symptoms and/or recurrences or worsening of symptoms changing with periods of incomplete or full remission. Generally about 86% of MS patients have a RR form, at least in the beginning [169].
2. **Secondary progressive (SP):** The majority of patients with RR change to a course of more gradual functional loss and increasing disability, without significant remission.
3. **Primary progressive (PP) (sometimes called chronic progressive from onset):** These patients have a progressive course from onset, with a more gradual and steady deterioration. About 15% of a patient population present this course.
4. **Benign MS:** These patients have a RR-course but do not develop significant disability (Expanded Disability Status Scale (EDSS) [93] $\leq$ 3,0) during the first 10-15 years from onset.

It is important to point out that this is only a general description of some categories which authors may have different definitions and opinions about. In spite of clear definitions it may be difficult to place the individual patient in any of the categories. The benign category differs from the others in the time limit, which implies that it is first possible to categorise benign MS ten years or later after onset of the disease.

2.4. Brain imaging

Advances in neuroimaging, in particular magnetic resonance imaging (MRI), have made a major contribution to the investigation of MS. Computerised tomography (CT) was the first method to visualise MS plaques in vivo. CT demonstrated discrete low attenuation white matter lesions, but in a limited number of MS patients [113]. The first report on MRI included a comparison with CT and showed that MRI detected about 10 times more lesions than CT [194]. The MR image is derived from the nuclear magnetic resonance (NMR) signal obtained while the subject is placed in a strong magnetic field.

The use of MRI in MS has provided a great amount of information about the number and distribution of lesions in MS patients. However, although MRI has proven to be highly sensitive to MS lesions, most studies found little or no correlation to neurological disability (e.g.[10,49,54,193]). Standard neurological rating scales are not sensitive to lesions in all areas of the brain and this might explain the poor correlation. Neuropsychological studies generally report significant associations between neuropsychological index scores and measures of MRI total lesion burden (TLB)[33,54,143,155,183], although exceptions exist[71]. Recent studies have reported associations between lesion burden in a specific region of the brain (e.g. left frontal lobe) and specific cognitive impairment (e.g. impaired abstract problem solving, memory, and word fluency)[6,183]. The overall picture shows generally stronger correlations for cognitive scores than neurological rating scores, but the correlation coefficients are often low and the results are not unambiguous.

There are several possible explanations for the weak associations between lesion burden on MRI and functional measures. Firstly the enormous variability in MS makes group size, time since attack, course of disease, and other variables, very important for the results. Secondly, differences in accuracy of measuring the lesion load using quantitative or semiquantitative assessment are crucial for the results [49]. Thirdly the content and the quality of the MRI signal influence what is imaged. The signals on conventional MRI are not specific to any of the major pathological features of MS, i.e. oedema, inflammation, gliosis, demyelination and axonal loss [49]. Persistent functional disability is more likely to be caused by demyelination or axonal loss, than for example oedema and inflammation. This might be one of the core reasons for the weak correlation between lesion load on MRI and neurological disability. Other MR techniques (e.g. magnetisation transfer or positron MR spectroscopy) provide better indirect information about the amount of destruction within brain tissues, and show a better correlation to functional loss [58,111]. In addition, normal-appearing white matter on conventional MRI in MS patients shows alterations using magnetic transfer[48], which might cause otherwise unexplained functional impairments. Finally, some of the studies did not correct the neuropsychological scores for age and education, which might cause artefacts.

In a rather limited number of studies Single Photon Emission Computer Tomography (SPECT) and Positron Emission Tomography (PET) were used in MS patients. These techniques both involve the injection of a radioactive isotope into the blood. Through the blood the isotope is transported to and distributed throughout the brain. The emission of the radioactive agent from various regions of the brain is detected by a camera. In SPECT single photons emitted from the externally administered tracer are detected by a number of detectors in a ring around the head. This information about regional activity from three dimensions is registered in a computer and used to construct pictures of regional activity (e.g. blood flow) in the brain. PET scans use another physical principle. When positrons are realised from the radioactive tracer and collide with electrons, they annihilate each other. This is results in two gamma rays, each moving in exactly the opposite way (180°) of the other through the skull. By the detection of such coincident gamma signals on opposite detectors placed around the head, it is possible to compute pictures of regional activity in the brain. Figure 2.2. illustrates a MRI and a PET image from a MS patient, compared to a PET image of a healthy control subject. SPECT is most widely used to measure blood flow, whereas PET is also used to measure glucose metabolic activity and neurotransmitter function. The resolution of PET is better than that of SPECT, but SPECT has the advantage of being much cheaper.

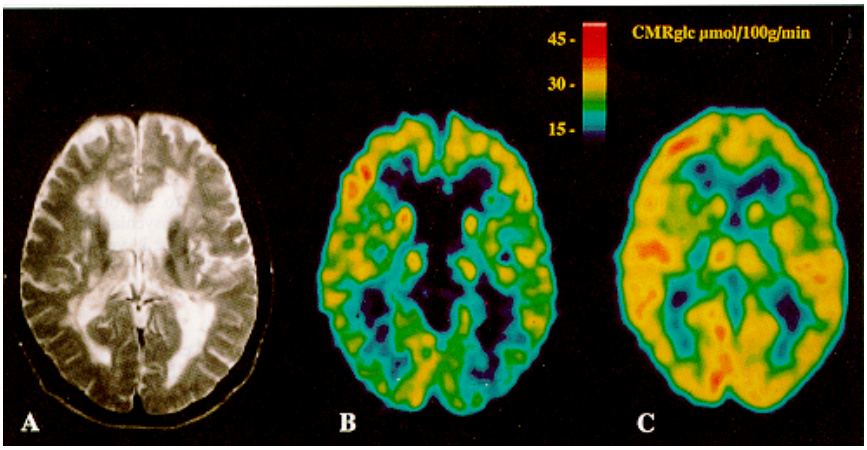

Figure 2.2. Co-registered MRI (A) and PET (B) images from a MS patient and a PET image of a representative normal control (C). The MRI shows enlarged ventricles and excessive periventricular plaque formation. The PET image of the patient shows global reduction of glucose metabolism, with the lowest values bilaterally in the thalamus and in the temporo-occipital region (from Blinkenberg et al.[26]).

In one of the first PET studies Brooks et al.[28] found significantly reduced metabolic rate of oxygen in white and grey matter in 15 MS patients compared to normal subjects. There was a significant association between cerebral metabolism and full scale IQ, but not with measures

of locomotor function. Pozzilli et al [134] found no differences in total supratentorial glucose metabolism between patients with corpus callosum (CC) atrophy, with no CC atrophy and controls. Only patients with corpus callosum atrophy showed significantly lower metabolism in the left frontal, temporal, and parietal cortex, compared to the right, in spite of symmetrical distribution of MRI-detected lesions. Other studies have shown that MS patients in an early phase of the disease exhibit a significant decrease in CC area, and furthermore CC atrophy have been reported in MS patients with mild and absent brain atrophy. This suggests to Pozzilli et al. that CC atrophy is not simply an element of diffuse brain atrophy, but may be an early sign of the disease process. Paulesu et al.[128] examined the functional basis of memory impairment in MS. Relative to healthy controls, MS patients with memory impairment showed a significant bilateral reduction of metabolism in the hippocampus, cingulate gyrus, thalamus, associative occipital cortex and cerebellum. Compared to memory unimpaired MS patients, the memory impaired patients had lower metabolism in the left thalamus and both hippocampi.

In a recent study Roelcke et al. [154] investigated the pathophysiology of fatigue in MS using PET. Global metabolism was significantly lower in a MS group with fatigue and a MS group without fatigue, compared to normal controls, but was not related to fatigue severity. Compared to the MS group without fatigue the metabolism in the MS group with fatigue was reduced bilaterally in lateral and medial prefrontal cortex and adjacent white matter, premotor cortex, putamen and in the right supplementary motor area. The study thus indicates that fatigue in MS is associated with frontal cortex and basal ganglia dysfunction. Finally a study by Jansen et al.[73] measured the active plaques by a calcium tracer (^{55}Cobalt) sensitive to the calcium flux in active lesions. This is a more direct measure of cell death, and the number of lesions detected by Cobalt-PET correlated significantly with MS progression.

SPECT has only been used in a few studies. A SPECT study by Pozzilli et al.[135] revealed reduced blood flow in the frontal lobes and the left temporal lobe of MS patients with cognitive dysfunction. A relationship was found between reduced blood flow in the left temporal region and deficits in verbal fluency and verbal memory. Lycke et al.[102] reported a similar correlation between frontal hypoperfusion (SPECT) and impaired cognitive functions, most significant for MS patients with a progressive course compared to relapsing remitting.

In conclusion, MRI is widely used in MS patients and this technique has proven to be particularly sensitive to pathological changes in MS. However, the correlations between lesions on conventional MRI and clinical measures are often only modest. This might be explained by poor accuracy of measurement, the nature of the MR signal, properties of the rating scales and methodological problems. Functional brain imaging has until now been used only in a limited number of studies. These studies indicate widespread changes in the regional cerebral metabolism and regional blood flow. Some studies indicate a correlation between specific neuropsychological impairment and reduced metabolism or blood flow in critical brain structures.

2.5. Mood disorders

Though it is recognised that a description of mood disorders traditionally follows the description of cognitive functions, the section is placed here, because mood disorders in this study is regarded as a background variable.

MS affects young people in an active period of their lives and the disease often results in marked alterations of plans for the future - children, marriage, education, career etc. Therefore MS patients demonstrate a broad range of reactions, both in relation to the diagnosis and later on in the course of the disease. There has been a long debate whether the emotional changes are psychological or biological in origin. MS lesions may directly lead to brain damage and dysfunction to some extent. However, reports do indicate a correspondence between severely threatening events at onset or exacerbation in MS[61], and the existence of different psychological coping styles[27]. There seems to be multifaceted interactions between environmental and organic factors in the causation of emotional disturbances. Some, but certainly not all, of these reactions can be described as psychiatric conditions - euphoria, depression, bipolar affective disease, psychosis.

Euphoria

For the last 100 years euphoria has been one of the most controversial psychological aspects of MS. In 1920-30 some influential papers reported symptoms of euphoria in more than 70% of the MS patients[138], and these results coloured the teaching and writing of MS until

recently. Since 1930 a number of studies published lower, but rather divergent, prevalence rates of euphoria (0-54 %)[117,139,182]. There are some possible explanations of this divergence. Euphoria has a variety of meanings and has often loosely been used to characterise all sorts of emotional disturbances in MS. Euphoria should be distinguished from "(hypo)mania" (associated with hyperactivity, pressured speech, and racing thoughts) and "pathological laughing and weeping" (associated with the patients' lack of control of their outward expression of emotion)[117]. Euphoria has often been defined as "a sustained cheerful mood", but a more precise and operational definition is still lacking [138]. Euphoria has to be distinguished from the old concept of "eutonia", which may refer to a state of "unconcern and unawareness" [138]. Part of the differences among prevalence rates might therefore be attributed to conceptual differences. Other explanations might be differences between the study samples in severity, course and duration of disease.

"True euphoria" is most likely a neurologically based state and not caused by psychological factors [117,138]. Rabins et al.[139] reported euphoric patients to have larger brain involvement, enlarged ventricles and relapsing-progressive or progressive MS, compared to non-euphoric patients. Corticosteroid therapy sometimes causes transient elevation of mood and should not be misinterpreted as euphoria[156].

In summary, although euphoria was earlier considered a hallmark of MS, its true prevalence and natural history still remains unknown. However, there is no doubt that the presence of euphoria in MS has been exaggerated. Euphoria is closely related to pathology of the brain.

Depression

Among psychiatric disorders in MS, depression is the most frequent. Since 1950 a number of studies have searched for prevalence rates of depression in MS. These studies differ in sample size, research design, measurement of depression, use of control groups, etc. In a comprehensive review Minden and Shiffer[117] suggested the point prevalence of significant depression, in studies using reliable and valid methods of measurement, to range between 27% and 54%. Recent studies seem to confirm this level [160,181]. Depression in MS is typically moderately severe and patients tend to be angry, irritable, worried and discouraged, rather than self-critical, withdrawn, and uninterested[117].

The association between depression and neurological disease seems to be more complicated than is the case for euphoria. There is some evidence to support the view that depression is a neurologically based disorder. MS patients experience depressive disturbances more often than the general population[160] and patients with other neurological diseases[139,192]. Patients with primarily cerebral involvement appear to be more depressed than do patients with primarily spinal cord disease[139]. A recent study of depressed and non-depressed MS patients, matched for lesion location and load, showed significantly different regional cerebral blood flow distribution in the limbic cortex of depressed MS patients[159]. However, other data argue against a simple organic explanation for depression in MS. There is no direct association between depression and brain involvement[35,44,79] and Shiffer[162] even found a better outcome of treatment for depression in patients with significant disease activity. There is no support for a dominating genetic component in near relatives of MS patients[43,69,160,181]. Depression in MS covers a broad spectrum and studies of psychological coping styles indicate that complicated psychosocial dynamics play an important role[27].

In summary, a number of studies indicate that between a fourth and half of the MS patients are at risk of developing depression during their lifetime. This risk of MS patients seems to be higher than the risk for the general population and groups of patients with other neurological disorders. Biological, psychological, and social factors interact in some way, but the cause, or the causes, of depression in MS still remains unclear.

Bipolar affective disorder

A number of anecdotal reports indicate a correspondence between MS and mania[117]. Shiffer et al. [168] searched hospital and Multiple Sclerosis Society data bases for residents who had both MS and a diagnosis of bipolar disorder. They reported a lifetime risk for bipolar disorder among MS patients in a specific New York area which was twice the risk in a comparable population free of neurologic disease. In another study Joffe et al.[79], using a standardised psychiatric assessment of 100 consecutive MS patients, found 13% who met the criteria for bipolar disorder. Compared to 1% of bipolar disorder in the general population the frequency in the MS group was quite high. The studies of bipolar disorder in MS are fewer than studies of unipolar disorder, but bipolar disorder is less common than unipolar depression. In

addition, the clinical symptoms are less likely to be mistaken for such neurological symptoms as fatigue, lack of energy, and weakness, making the diagnosis more precise. In conclusion, the knowledge of bipolar disorder in MS is based on rather few studies, which concurrently indicate an unexpectedly high prevalence of bipolar disorder.

Psychosis

Psychoses are relatively rare in MS compared to other psychiatric manifestations[103]. In a few cases, MS seemed to begin with an acute remitting psychotic episode[26,104] or a chronic atypical psychosis[87]. Feinstein et al.[46] studied psychotic illness in MS. Only 10 patients with definite MS and a MRI scan were referred to the psychiatric department of the National Hospital in London over a period of 6 years. These 10 psychotic MS patients were compared with 10 MS patients without psychosis, matched retrospectively with respect to age, disability, duration of symptoms, and course of disease. The psychotic group had a higher total lesion load, particularly around the temporal horn, and they were older at onset of psychosis than patients without brain disease. The findings indicate that MS lesions may play a role in the pathogenesis of psychosis in MS.

3. COGNITIVE DYSFUNCTION IN MS

3.1 Frequency of cognitive dysfunction in MS

The true prevalence of cognitive impairment in MS remains controversial. The early belief that cognitive disturbances in MS are rare seemed reasonable in light of studies published at that time. Large-scale epidemiological studies and other studies based on clinical examinations indicated only relatively small percentages of cognitive dysfunction among MS patients [68,80,95,140]. One example is Kurtzke et al. [95], who published results in 1972 from an examination of 487 men from the US Army with a diagnosis of definite MS. On clinical examination, “only 2.9% had any impairment of mentation, and this was mild”. However, during the past decades there has been a tremendous increase in the prevalence rates reported in neuropsychological studies. Today a more realistic prevalence rate is assumed to be somewhere between 40 and 60 % [11,103,130,142].

Although the general belief until ten years ago was that dementia was seldom in MS, 9 of 11 studies reported prevalence rates of 50-60% between 1957 and 1986 [130]. However, in more than half of the studies prevalence rates were based on less than 50 patients, and not all studies used comprehensive neuropsychological testing. It does not seem reasonable to make prevalence generalisations from studies based on very small and often biased populations. This review is based on MS studies published since 1985 which include 50 or more patients, and which contain information about the prevalence of cognitive dysfunction. Not all the studies are primarily concerned with the prevalence, but do report prevalence rates based on extensive neuropsychological testing. Although the studies differ in design and methods, they may be used to give an impression of the level of the true prevalence of cognitive impairment in MS.

A number of studies used brief cognitive screening procedures to identify patients with cognitive impairment. A very popular test is the Mini Mental State Examination (MMSE) [52], which is often used because it is reliable and easy to administer (5-10 minutes). If 28 is used as the cut-off score, the MMSE classifies approximately 20% of MS patients as demented, but using the recommended cut-off score (usually 24), the test is almost completely insensitive[12,54,142]. Beatty et al. [12] examined the sensitivity and specificity by comparing the

MMSE score to the results of an extensive battery of neuropsychological tests. The general specificity was quite high, but at a score of less than 28 on the MMSE only about 65% of the patients with dementia were correctly classified. Other studies reported a sensitivity of brief screening instruments at almost the same level (i.e. [68,80]).

In a recent study Beatty et al. [20] tested a new brief screening battery, the Screening Examination for Cognitive Impairment (SEFCI), lasting about 25 minutes. 103 community-dwelling MS patients completed the SEFCI and a neuropsychological test battery (lasting about 2-hours). MS patients were compared to a group of 32 normal controls with the same mean age and years of education as the MS patients. Defining impairment as performance below the 5th percentile of normal controls on at least one of the four tests in SEFCI, 52% of the patients were impaired. Using the results from the neuropsychological test battery as criterion for cognitive impairment, the sensitivity of SEFCI was 86% and the specificity 90%. This study very well illustrates the marked increase in sensitivity which can be achieved at a relatively low time cost.

In order to assess the true prevalence of cognitive dysfunction, it is necessary to use more sophisticated methods. Heaton et al. [68] were among the first to use more extensive neuropsychological testing on large-scale MS groups, although this study did not intend to report the prevalence rate of cognitive dysfunction. The potential study sample consisted of 172 consecutive admissions to the local MS centre with no history of other neurological illness, significant head trauma or substance abuse. Among the potential cases 10 refused to participate, 28 were excluded due to a stormy disease course and finally 34 with severe MS were excluded because they were not capable of performing the test battery. The final study group consisted of 100 MS patients with a mean age of 37,4 years, a F/M sex ratio 3,0, and a mean disease duration of 9,4 years. Neurological disability was measured by DSS (mean 3,1). 57% of the patients had a Relapsing Remitting (RR) course of the disease and 43% a Chronic Progressive (CP) course of disease. All subjects were administered the WAIS, the standard Halstead-Reitan Battery (HHB), and 10 additional neuropsychological tests. The patient group was compared to 100 healthy controls matched on education but not on formal age and gender. Data analysis was mainly based on group by group comparisons between patients with relapsing-remitting MS, chronic-progressive MS and healthy controls. In the results

section it is mentioned that 57% of the MS patients were impaired on neuropsychological testing, but the criteria for this “impariment” were not specified.

Comi et al. [33] evaluated the correlations of MRI and cognitive impairment in MS. 64 of 186 MS patients consecutively admitted to a MS centre completed a full neuropsychological test battery. Background data were not described for this subgroup of patients. A total of 122 patients were excluded from a neuropsychological evaluation because of severe physical impairment, drug abuse, personal reasons or lack of cooperation. Wechsler Memory Scale, WAIS, Token Test, Judgement of Line Orientation Test and a Cancellation Task were used. The performance in WMS and WAIS were considered to be abnormal below a cut-off of 89, and for the remaining tests the cut-off was set at the 10th percentile. There was no control group, but instead relevant published standards, adjusted for age and education, were used. Cognitive impairment was considered to be severe if two or more tests were abnormal or if WAIS or WMS scores were less than 79. Cognitive impairment was considered mild if only one test was abnormal. Degree of impairment was mild in 22 % and severe in 25 percent of the patients, meaning that 47% of the patients were considered to be cognitively impaired.

Amato et al. [3] studied the cognitive development over a 4-year period. The 50 MS patients were participants in the Italian Multicenter Prospective Study on the Prognosis of MS [173]. At the beginning of the study, the mean disease duration from clinical onset was 1,6 years and the neurological disability was low (EDSS mean 2,6). 88 percent of the patients had a RR course and 12 % had a CP course of disease. Hamilton Depression Scale (HDS) revealed no differences between the groups at the initial testing. At the time of follow-up testing there were significantly more depression in the MS group than in the control group. All participants completed a comprehensive neuropsychological battery twice (9 tests). Impairment was defined as scores below the 5th percentile of a group of 70 controls (NC) matched on age, gender and education. The normal controls failed on average 1,8 (±1,4) test, which seems strange with the 5th as criteria for a failed test. MS patients failed significantly more tests than NC both at the initial examination (mean 3,2 (±3,7)) and at the follow-up examination after four years (mean 3,8 (±3,3)). Excluding all depressed subjects (HDS cut-off score 13) still revealed significant differences in cognitive function between the groups. At the first examination 78% of the patients failed two or more tests and after four years 100% failed two

or more tests. The study indicates that cognitive impairment may be frequent early in the course of MS, but compared to other studies the frequencies of cognitive impairment are surprisingly high.

In two of the studies with mini mental status examinations referred to above, additional comprehensive neuropsychological tests were used. In the study using SEFCI (by Beatty et al. [20]), the neuropsychological test battery revealed severe cognitive impairment (below the 5th percentile of normal controls (n=32) on 3-7 tests) in 42% of the patients. An additional 39% of the patients exhibited impairment in one or two tests. The results have to be interpreted with some caution, due to the limited number of normal controls and a high proportion of the patients receiving medication that might affect their performance. In the other study Franklin et al. [54] examined 60 patients with chronic/progressive MS admitted to a multi-center trial of the drug Cyclosporin A. The MS patients had a mean age of 37 years, a mean disease duration of 14,6 years and an average EDSS score of 5,3. The F/M sex ratio was 1,7. As part of the baseline examination before the trial, the patients completed a neuropsychological screening battery (NRS) of 15 well-known neuropsychological tests. The performance of the MS patients was compared to the performance of 60 neurologically normal control (NC) subjects matched on age, gender and educational level. Mild impairment (1 impairment point) was defined as scores 1 standard deviation below the mean of the NC group, and severe impairment (2 impairment points) as scores below the bottom 5th percentile of the NC group. A cognitive summary score was computed by adding the impairment points across the subtests that require minimal upper-extremity skills, revealing that 60% of the patients were significantly impaired.

MS patients in the studies mentioned so far were all recruited from various kinds of MS clinics. This might cause a selection bias towards patients with greater disability and more active disease than the general MS population. Two studies tried to evaluate this potential bias. McIntosh-Michaelis [108] examined 147 MS patients from a population-based register - age mean 48 years, disease duration mean 13 years, EDSS (mean 6,0) and sex ratio F/M - 3,0. The patients were interviewed and tested in their own homes by the same psychologist. The neuropsychological test battery was chosen to be independent of motor function: The Rivermead Behavioural Memory Test (RBMT), Wisconsin Card Sorting Test (WCST),

Verbal Fluency (VF), Raven´s Standard Progressive Matrices (RSPM) and six verbal subtests from the WAIS-R. Non-verbal IQ was estimated using RSPM. Cut-off scores were derived from standards published for the individual tests. General impairment was defined as: a) below the cut-off score on at least one of either the RBMT, VF, or WCST *and* b) at least one age-scaled verbal WAIS-R subtest below 7 and a between-subtest difference of 3 or more scaled points *and* c) an estimated non-verbal IQ of less than 90 or a within-subject RSPM A to E component discrepancy of at least 3. Based on these criteria general intellectual function was impaired in 22% of the patients, and 46% of the patients were impaired in one or more of the test areas. Memory and frontal lobe impairment was evident in about one third of the subjects.

Rao et al.'s [142] large-scale study of cognitive dysfunction in MS is probably the most cited in the MS literature. 100 MS patients were recruited at random from the membership list of a local MS society. They had an mean age of 45,7 years, a mean disease duration of 14,2 (±10) years, a mean EDSS of 4,1, and a F/M sex ratio of 3,0. All patients met the Poser et al. [132] criteria for definite or probable MS and had no history of alcohol/drug abuse or other nervous system disorder. Patients with severe motor/visual impairment and institutionalised patients were excluded. Over a 2-day period the subjects were given a neurologic examination, a MRI scan, and an ambitious neuropsychological examination. 27 well-known neuropsychological tests formed the test battery, which was designed to assess a wide range of cognitive domains: verbal intelligence, memory, abstract reasoning, attention/concentration, language, and visuospatial perception. A control group (NC) of 100 healthy adults, matched individually to the MS patients on age, education, and gender, completed the same neuropsychological test battery. The raw test scores for the MS and NC groups were converted to standardised residual scores to correct for individual differences in cognitive ability ([141]). The demographic variables (age, sex, education , and highest occupational level) were regressed with each cognitive test variable, resulting in the residual test score, which represents the difference between the subjects actual and predicted test scores. The 5th percentile residual score of the NC group was defined as the criterion for a "failed" test. The prevalence of cognitive impairment in the MS group was 40 %, defined as the percentage of MS patients classified as cognitively impaired minus the percentage of NC subjects misclassified as impaired.

Table 3.1 Studies of the frequency of cognitive impairment in MS.

Study	Number of patients	Matched controls?	Recruited from?	Prevalence of cognitive impairment
Heaton et al. [68]	100	YES/NO	Local MS centre	57%
Comi et al. [33]	64	NO	Local MS centre	47%
Pia Amato et al. [31)]	50	YES	Participants in a prospective MS study	78%[1)]/100%[2)]
Beatty et al.[20]	103	YES	Practices of neurologist and support groups	62%
Franklin et al. [54]	60	YES	Participants in a clinical trial	60%
McIntosh et al. [108]	147	NO	Population based register of MS.	22-46%
Rao et al. [142]	100	YES	Membership of a local MS society	40%

1) Initial examination 2) Follow up examination.

Table 3.2 Background variables

Study	Age mean (S.D.)	Disease duration mean (S.D.)	Neurological disability (mean)	Course of disease	Sex ratio F/M
Heaton et al. [68]	37,4 (8,3)	9,4 (5,9)	DSS 3,1	57% RR 43% CP	3,0
Comi et al. [33]	-	-	-	-	-
Pia Amato et al. [31)]	29,9 (8,5)[1)]	1,5[1)]	EDSS 2,0[1)]	88% RR 12% CP	1,8
Beatty et al.[20]	42,2 (9,3)	16,1 (9,6)	AI 3,5	-	1,7
Franklin et al. [54]	37	14,6	EDSS 5,3	100% CP	1,3
McIntosh et al. [108]	48	13	EDSS 6,0	-	1,8
Rao et al. [142]	45,7 (11,3)	14,2 (10)	EDSS 4,1	39% RR 19% CP 42% CS	3,0

Note: **(E)DSS: (Expanded) Disability Status Score, RR: relapsing remitting, CP: chronic progressive, CS: chronic stable. 1) Initial testing.**

Discussion

This review clearly demonstrates that cognitive impairment is frequent in different MS populations. However, as demonstrated in table 3.1 and 3.2, it is obvious that the studies differ in a number of methodological aspects, which might affect the results in different ways.

The majority of the studies used only normal control groups (except [33,108]), but normal controls do not adequately control for the possible effects of having a chronic disabling disease, use of medication, affective disturbances and hospitalisation [140]. The control subjects

were often matched to the patients with respect to gender, age and education, but two studies [3,108] used normative data from other sources to establish cut-off scores. In McIntosh-Michaelis et al. [108] raw scores were converted to percentiles using norms for the individual tests, but the use of demographic variables was different from test to test. This manoeuvre essentially makes the percentile scores incomparable between tests [7]. Only one study [142] corrected for individual differences in premorbid ability. The dominant criterion for a failed test was performance below the 5th percentile score of the control group, but the criteria for general cognitive impairment were defined in a number of different ways.

The method of recruitment of the patients is another important variable. The two population based studies tend to have lower prevalence rates than the other, which might be explained by selection bias in non-population based studies. The "true clinical spectrum" is distorted in various kinds of MS centres due to the selective omission of more severe or complicated cases. Furthermore, the clinical spectra between MS centres differ due to local geographical, political, and cultural conditions. In a study of referral bias in MS [122] a group of patients from a university research and patient care institution was compared to a population based group. Patients from the MS institution differed among other things in that: 1) they were younger, 2) they had more morbidity impairment for their age, and 3) disabled females were overrepresented compared to disabled males.

As a result of this bias, most studies potentially tend to overestimate the prevalence rates [130,140]. Patients admitted to the service of a MS centre probably have a higher neurological disability and suffer higher impact on daily living, than the general MS population. However, another bias working in the opposite direction might be present at the same time. The use of comprehensive neuropsychological testing as the only measure of cognitive impairment requires that the patients are able to complete neuropsychological tests. Consequently, most studies exclude patients with very high disability. Even in the two population based studies this bias might play a role. Rao et al. [142] excluded patients who resided in nursing homes and could not easily be evaluated at the medical centre. McIntosh-Michalis et al. [108]evaluated all subjects in their own homes and only two patients were too ill to co-operate. However, it is remarkable that almost 95% of this very heterogeneous group of MS patients were able to

complete demanding neuropsychological tests reliably (e.g. Wisconsin Card Sorting Test or Raven's Progressive Matrices).

The studies also differ on a number of other illness variables, which might affect the performance in neuropsychological tests. One such variable is the severity of MS, most often measured by the EDSS [93]. However, the majority of studies observed no or only a very weak correlation between the physical disability and cognitive performance (e.g. [20,54,105,108,141,142]). The tremendous symptom variability in MS might be one explanation of this weak relationship, but why do we expect this correlation to be strong? EDSS and Ambulation Index (AI) [66] are especially sensitive to pathology in the spinal cord and the motor/sensory system of the brain. Pathology in some of these areas is not necessarily expected to cause any cognitive symptoms. Likewise, in most cross-sectional studies no strong relationship is observed between duration of illness and cognitive impairment (e.g. [20,105,108,130,141,142]). At a first glance these results seem strange in light of the longitudinal studies observing an increase in the cognitive impairment over time [3,43]. However, the lack of relationship in cross-sectional studies may be explained by the large between-patient variability [140]. MS patients demonstrate a spectrum going from the newly diagnosed patient with severe cognitive impairment, to the patient with long duration of illness and no cognitive symptoms.

The disease course seems to play a role for the degree of cognitive impairment. It is a general finding that greater cognitive impairment occurs in patients with the chronic progressive (CP) course compared to patients with the relapsing remitting (RR) course (e.g. [14,33,47,68,142,183]), although there may exist a considerable group overlap [142]. Table 3.1.1. shows the large differences between the proportion of patients with CP and RR MS, and in 3 studies this important information was not even described.

It is not quite clear what effect medication may play for the performance in neuropsychological tests [140]. Rao et al. [142] found a nonsignificiant trend for medicated patients to fail more tests, while others did not (e.g. [20,68]).

Depression is relatively common in MS (e.g. [79,140]), but knowledge about the influence of depression on cognition is very sparse. Only two of the studies reviewed above consider this

relationship. Beatty et al. [20] and Rao et al [142] observed no significant relation between depression and cognitive impairment, although in the latter there was a trend for depressed patients to perform more poorly on cognitive tests. Conversely, a recent study of the influence of clinical variables in MS found a significant relation between the presence of cognitive dysfunction and depression [47]. There is a need for more research to illuminate the way depression influences cognitive performance in MS, but until then depression has to be considered as a potential source of error.

In conclusion, this review clearly demonstrates that research completed within the last ten years unequivocally points to a relatively high prevalence of cognitive impairment in MS. However, attempts to estimate the "true" prevalence of cognitive dysfunction are hampered by several methodological problems. Recruitment procedures, the number of patients, control groups, definitions of cognitive impairment and other clinical variables (i.e. neurological disability, course, duration, medication) are very different across the studies. These differences, and methodological shortcomings within the individual studies, make it difficult to compare the results and to draw any firm conclusion about the "true" prevalence of cognitive impairment.

3.2 DOMAINS OF COGNITIVE DYSFUNCTION

3.2.1 Memory

Most clinicians are familiar with MS patients who claim to have one or another difficulty in relation to poor memory function. They forget birthdays, miss appointments, forget to buy things in the supermarket, they can't find things at home, and so on. It is therefore not surprising to find memory dysfunction among the most frequent and consistently reported sequelae in the literature of MS.

Memory is probably the most widely studied cognitive function in the scientific literature. The ideas about human memory, its organisation and function, have undergone a major transformation during the past couple of decades[72,129,161,195]. It is now clear that in order to get a more comprehensive understanding of the concept of memory, it is necessary to distinguish between a number of qualitatively different subtypes of memory (see figure 4.2.1.). It is clear that the classic amnesic syndrome only impairs some aspects of memory, leaving other subtypes intact. This fragmentation of memory is important for a better understanding of the nature of memory dysfunction in MS.

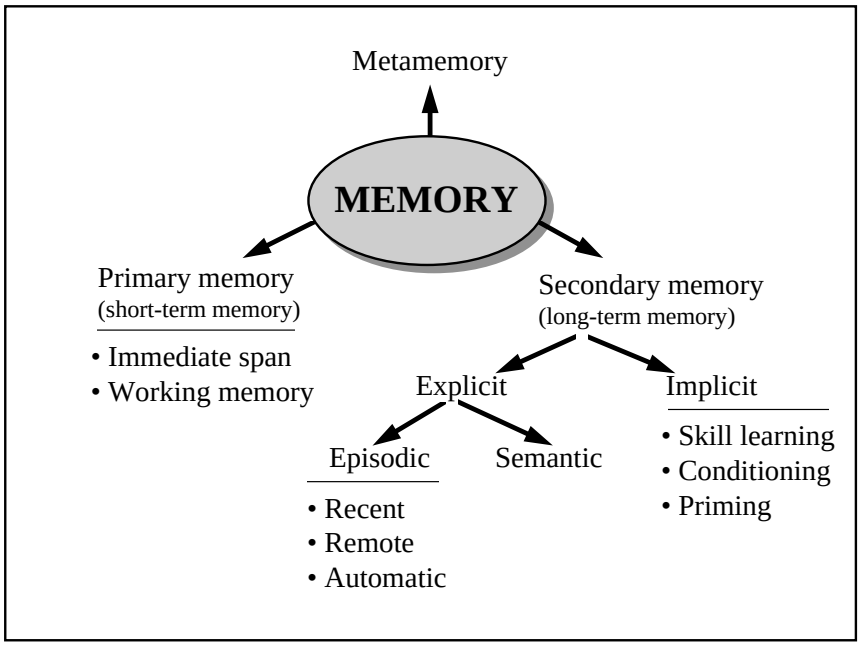

Figure 3.1. Fragmentation of the memory concept

Metamemory may be defined as “knowledge of one’s memory capabilities” and “knowledge of the strategies involved in memory performance” [72]. In the only study of metamemory in MS, Beatty & Monson [18] reported impaired metamemory in a group of 45 patients, indicating that MS patients’ self-reports about their memory capabilities may be unreliable sources of information. There will be no further discussion of metamemory in this review.

In 1986 Rao reviewed the literature concerning memory impairment in MS[140]. The general findings of this very comprehensive review were:

- All but one study found a normal capacity for immediate memory span, typically using the digit span test.
- Using a variety of memory tests, investigations generally found that MS patients’ ability to learn and recall information are impaired in comparison to normal controls.
- In general MS patients perform worse than controls on tests of delayed recall, but are not impaired to the same extent on tests of recognition memory.
- There is a large variability within groups of unselected patients, ranging from no apparent dysfunction to patients with severe memory impairment.
- MS patients acquire information at a slower rate than controls, but appear capable of incremental learning.

Since 1986 there have been a number of studies concerning different aspects of memory function in MS patients. The overall picture is still largely the same as described by Rao[140], but results from recent studies help to qualify some of the earlier findings. The following sections contains an update on some of the conclusions described above.

Primary memory

Primary memory generally refers to an immediate span (a very limited capacity storage for a short time (e.g. seconds to minutes)) or working memory. Baddeley and Hitch [9] described working memory as a more active process of transient storage and manipulation of information.

Until 1986 primary memory was found to be relatively intact, most often measured by digit span tests[140]. Using digit span tests some recent studies confirmed these results[74,82,99,105,144], but others did not[21,63,71,116,142], and the picture is no longer that clear. Another test of primary memory, the Brown Peterson Test, also reaches contradictory results. Grant et al [62] reported impairments in MS patients on this test. They found that MS patients recall of consonants trigrams was normal under conditions with either no delay or no interference, but significantly worse following an interference condition. Other studies did not find this impairment [15,20,99,142,144] (except Beatty et al. [17]) and procedural differences between the studies might simply account for these differences [15,99].

Some studies focused on the working memory component. Using the framework of Baddeley [9], Litvan et al. [99] found impairments at the level of the phonological loop in 16 moderately affected MS patients. Furthermore these patients were poorer at retrieving information from long-term store and in rapidly processing verbal information. Ruchkin et al. [157] examined 10 MS patients with mild physical symptoms. using experimental working memory tests and event-related potentials (ERP). The results indicated that verbal working memory was especially susceptible to impairment, while spatial working memory was less susceptible. This might be due to the impact of MS upon white matter pathways transmitting information between the posterior phonological loop and the anterior phonological output system.

Secondary memory

Tasks that require the recall or recognition of informational units exceeding the capacity of primary memory are in general considered to involve some kind of secondary memory. In 1986 Rao [140] found delayed recall and recognition to be consistently impaired, reviewing studies measuring primarily learning and retrieval of verbal material. Since then there have been a large number of memory studies e.g. [15,99,142,144] and other studies [54,71,74,82,105,155] replicating these results. It seems therefore reasonable to conclude that MS patients in general are poorer than controls in verbal learning and retrieval of verbal information. The same seems to be true for non-verbal material [49,54,82,116,142], although visual disturbances often complicates the examination of this cognitive function.

These studies, however, only cover a very limited aspect of secondary memory (see figure 4.2.1.). Beatty et al. [16] wanted to see if MS patients performed like patients with prototypical "subcortical" dementia (Huntington's disease) and "cortical" dementia (Alzheimers disease) on tests of implicit memory. For example, patients with Huntington's disease are known to exhibit deficits in acquiring motor skills, but perform normally on lexical priming tasks, while Alzheimer patients show the reverse pattern. Compared to normal controls 20 chronic progressive MS patients were impaired on explicit tests of verbal recognition memory, but showed normal pursuit rotor learning and normal priming on a stem completion task. The pattern of cognitive dysfunction appeared to be unique and did not typify either cortical or subcortical dementia.

Testing another memory dichotomy, automatic versus effortful, Grafman et al. [60] found that MS patients were significantly impaired on memory tests requiring effort, but performed normally on measures of automatic memory (frequency information). This discrepancy could possibly be explained by an impairment in the effortful strategic aspects of searching long-term memory. An alternative explanation might be limitations in working memory which disturbs the temporal storage within a rehearsal loop for later processing. However, another study using a free word association test to distinguish between automatic and effortful memory found no impairment in 33 moderately impaired MS patients [131].

Semantic memory refers to our knowledge of facts and relations between objects in the world (e.g. Clinton is the president of USA, London is the capital of England). The semantic memory of MS patients is not particularly well characterised. In a very interesting study Goldstein et al. [59] examined gist recall, which is the memory for important story ideas. 12 MS patients were read prose passages from the Wechsler Memory Test, containing low, medium and high information content. Compared to normal controls the immediate and delayed total recall of elements were lower for the patients. However, like the control subjects, they recalled more ideas that were of high, rather than low and medium importance, suggesting an intact semantic sensitivity for important features of narratives. Although the results are based on a very limited number of patients, it is noteworthy that this shift of focus from quantitative to qualitative aspects of memory reveals some very interesting information.

Remote memory was studied by Beatty et al. [17], who administered the Famous Faces Test to chronic progressive MS patients. The patients had to identify famous faces from the 1940s through the 1980s. In general MS patients were found to be impaired relative to controls on this test, and the impairment was equally distributed through the decades (flat gradient). The same remote memory impairment was found in patients with relapsing remitting MS [15] and in the general MS population [142]. An analysis in the Beatty et al. study [15] found it unlikely that inability to recall past events or famous people, is secondary to impairments in anterograde memory.

Discussion

Memory impairment is apparently a striking feature of MS. However, it is not possible to conclude that memory is directly affected, without considering other illness factors of interest. High prevalence rates are reported for depression (i.e.[11,79,156]), but memory impairment can in general not be attributed to depression [15,17,49,116]. Also severity of disability, measured for example by DSS or EDSS is, except in a few studies, not found to be correlated with memory impairment [15,49,116]. Patients with chronic progressive MS (CP) perform worse than patients with relapsing remitting MS (RR) on various measures of memory function [15,49,116]. However, patients of the CP type are often older and have longer time since onset than RR patients.

A long lasting controversy in MS research concerns the specific nature of memory disorder in MS[21,39,144]. Is the memory disorder caused by retrieval or acquisition failure? The retrieval hypothesis is supported by the frequent finding that recognition memory is better than free recall (e.g. [39], indicating that information is stored in the brain, but that the patients can't find specific information on request. The very consistent finding of poor performance on fluency test also supports this hypothesis. Alternatively, the acquisition hypothesis states that information is acquired at a slower rate, but once acquired, memory is almost normal. This hypothesis is supported by studies suggesting that the memory impairment may be caused by impaired working memory capacity [99,157] and slowed information processing speed [17,98]. There is still no answer to the question and maybe there never will be an appropriate solution. It might simply be misleading to put the question just like that, because it implies the existence of a unitary memory disturbance in MS.

Beatty et al [21] address this problem in a recent and very interesting study. A group of 99 MS patients, recruited from neurologist and MS support groups, had the Selective Reminding Test (SRT). Using six different cluster analysis methods the results consistently indicated three distinct patterns of SRT performance: Approximately 25% performed normally, 22% exhibited a severe amnesia-like disturbance and the remaining 53% showed mild to moderate memory impairments. In another analysis "prototypes" of "pure retrieval" and "pure acquisition" disorder were defined using conservative operational criteria. "Pure retrieval disorder" was for example defined as performance below the 5th centile of normal controls on Sum Recall, Delayed Recall, and Consistent Long Term Retrieval, but above the 5th centile on Long Term Storage and Delayed Recognition. Only two of the patients met all the criteria for a "pure retrieval disorder" and only four patients met the criteria for a "pure acquisition deficit", indicating that neither of these characterisations are able to describe the nature of the memory impairment for the majority of MS patients.

After this short review of the literature, it seems safe to conclude that memory impairment is a major feature of MS. The conclusions from Rao´s review [140] mentioned earlier still seem to be relevant, although they need to be updated in light of recent research:

- Most, but not all, studies found normal performance in tests immediate memory span.
- A number of recent studies indicate impairments at the level of the phonological loop in tests of working memory.
- The general disturbance in episodic memory has been replicated in a large number of studies. However, recent studies indicate that other aspects of secondary memory are unimpaired - e.g. implicit memory, automatic memory and some aspects of semantic memory.
- No single memory deficit seems to offer an adequate explanation of the nature of memory disturbance in MS.

3.2.2 Attention and speed of information processing

Attention is the ability to deal with the constant stream of incoming stimuli and among the most critical abilities for purposeful and goal-directed human action. We are confronted with a huge amount of information, and need only focus on a very limited part of this informational flow. Various models of attention propose the existence of qualitatively different attention processes [42,109,133]. Recent studies, using brain mapping under cognitive activation, also indicate the existence of different attention processes, illustrated as activation and deactivation in distinctive patterns of brain regions (i.e.[23,37,126,127]). However, for the purpose of this short review, attention is divided into three types: Focused attention, divided attention and sustained attention. *Focused or selective attention* refers to the process of keeping the mental focus on one stimulus among others (sometimes called the "cocktail party" problem). *Divided attention* refers to the simultaneous processing of two or more things. The capacity to process information plays a major role and therefore *speed of information processing* is often closely linked to this kind of attention. Finally *sustained attention* is the stability in maintaining attention over time and refers to a qualitatively different aspect of attention.

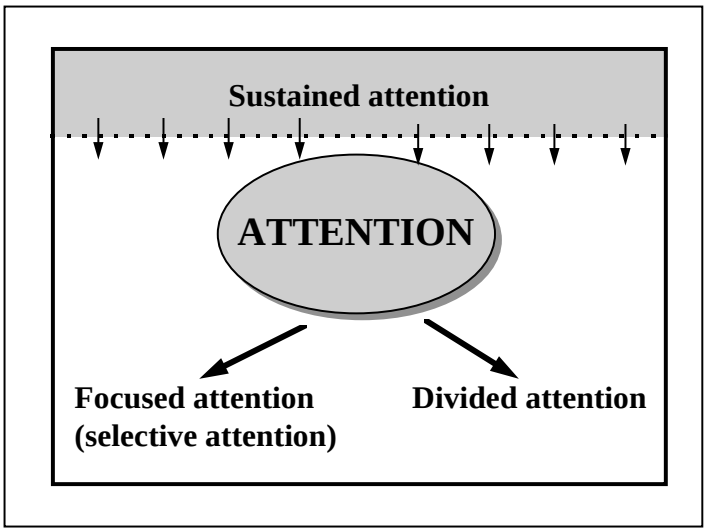

Figure 3.2. Model of attention

Rather few studies in the MS literature are mainly concerned with attentional topics and the nature of the attentional deficits in MS is not very well understood. In Rao´s [140] comprehensive review, attention occupies less than half a page. However, a number of studies

have been published during the past 10 years, making it possible to get a slightly more precise picture of attention processing in MS

Focused attention

Divided and focused attention are two theoretically formed concepts which are often difficult to separate in relation to a concrete task. For this purpose focused attention is defined as the ability to pay selective attention to one cue among others. The Stroop Test is considered a classical test of this cognitive function, involving the naming of first colour congruent and then colour incongruent words. In the majority of studies, MS patients performed significantly below normal controls in the interference part of this test [45,74,75,90,142,185] (one exception is [186]). Other tasks which put high demands on focused attention are cancellation tasks, where the subject has to identify a specific digit or letter among others. Franklin et al. [54] used a 1-page digit cancellation task in a study of 60 chronic/progressive MS patients. Compared to normal controls the MS patients were significantly slower, but a difference in errors was not significant. In a recent study by Filippi et al [47] only 2,4% of the patients performed below the 5th percentile of normal controls on a cancellation task. However, it was not described whether time, number of errors or both were used as criterion. A slightly different variation of letter cancellation is the letter counting test. Ron et al. [155] found MS patients to be impaired on such a test.

Divided attention

The concept of divided attention refers to the ability to pay attention to two or more things at the same time. This cognitive capacity is very central for most human activities and impaired divided attention may result in a severe handicap for the patients. The Paced Auditory Serial Addition Test (PASAT) is often used as a measure of divided attention. In PASAT the subject is presented with random series of digits at different presentation rates, and then has to add the current digit to the one immediately preceding it. A number of studies found that MS patients performed below the level of normal controls in the PASAT, especially in the hard trials [40,45,90,98,142,146]. Another test which also put high demands on the simultaneous processing of information, is the Sternberg Memory Scanning Test (SMST). First the subject is asked to memorise a set of 1-4 digits, and then a number of single digits are serially presented on a computer screen. The task for each digit is to decide whether the stimulus

match one of the digits held in memory. There seems to be a linear relationship between the response speed and size of the string held in memory [176,177]. The slope of the reaction time is often considered as a relatively pure cognitive measure of the time it takes to compare the test stimulus to the string of digits held in memory. In a study of 16 patients with MS, Litvan et al. [98]did not observe any change in the slope. Two studies by Rao et al. [142,146], using larger patient samples, showed a significantly slower scanning rate for MS patients compared to healthy controls.

A decrease in the s*peed of information processing* is often considered a symptom of limitations in the capacity to process information. For example, most MS patients display impairments in the Symbol Digit Substitution Test and the Trail Making Test (e.g. [15,51,54,82,88]). However, simple motor function plays a major role in tests like these, and make them unfit for use in MS groups with very heterogeneous motor disability. Poor motor ability simply overrides the focus of the test, namely the psycho-motor co-ordination. The disproportionately high standard deviations of MS patients in the difference between Trail A and Trail B illustrates this problem very well (e.g. [54]).

Evidence from simple and choice reaction time (RT) measures has been reported in a number of studies. Elsass and Zeeberg [41] reported delayed continuous RT´s in 50 MS patients, compared to normal controls. The reaction time was significantly correlated with degree of disability, and patients in a progressing course of the disease had slower reaction times than patients in remission. Jennekens-Schinkel [76,77] measured simple visual/auditory RT and visual/auditory "go - no go" RT in 39 patients with relatively mild MS and 25 healthy controls. In general, RT's were significantly longer in MS, and the increase in RT was related to disease duration, but not to age. There was no relation between the RT pattern and variables of task complexity. Feinstein et al [45] also reported prolonged simple and choice RT´s in five MS patients. Rao et al. [142] used the difference between simple and choice RT, which probably better reflects the cognitive component, but found no difference between MS patients and controls.

Studies of RT demonstrate a clear tendency of slower information processing in MS patients, but nothing about the reason for this slowness. The study by Rao et al. [142] even questions

whether the impairment is cognitive in origin. In a recent study Kujala et al. (17202) evaluated this problem. Using computerised tests they investigated three separate stages of information processing (automatic and controlled processing, and motor programming) in 45 MS patients and 35 healthy controls. The patients were divided into a group with mild cognitive deterioration and a group with preserved cognitive capacity. Patients with mild cognitive impairment were slower than patients with preserved capacities and healthy controls in every stage of the information processing. The patients with preserved capacities also showed signs of mild slowing in automatic visual processing. The study indicates that the slowness of information processing, even in patients with mild cognitive impairment, may be cognitive in origin.

Sustained attention

Fatigue is one of the most common complaints reported by MS patients, and might be considered an aspect of sustained attention. Here sustained attention is defined as the ability to remain attentive over time. Traditionally sustained attention is measured by relatively long lasting and simple signal detection tasks. MS patients' performance was deficient in a study of the Auditory Attention Test, requiring the subject to recognise the letters of the alphabet in their correct order when presented auditorily embedded in a random string of letters [155]. Filly et al. [51] reported impaired performance of MS patients in a similar kind of digit vigilance test.

Two recent studies evaluated sustained attention in MS groups differing in cognitive status. Kujala et al. [90] used a visual vigilance test requiring the subject to detect targets (letter Y & L) among 600 letters presented on a computer screen with 100 ms interval. On the basis of their performance, the 45 MS patients were allocated to a group of patients with preserved cognitive ability (n = 23) and a group with mild cognitive deterioration. The mildly deteriorated group observed fewer targets, made more errors and exhibited slower reaction times than the cognitively preserved and the normal controls. The group with preserved cognitive ability performed in general like the controls, except for significantly longer reaction times in the last two thirds of the test. In another study Jennekens-Schinkel [76,77] evaluated the effect of prolonged effort (four hours of neuropsychological testing) using four different RT measures. As described above the MS patients were generally slower, but there was no significant change in performance between the first and second measurement.

Subjectively the MS patients experienced an effort-related fatigue. It can be questioned whether this study design is suited to test this kind of fatigue at all. The sample of ambulant MS patients might simply have the resources to compensate for the negative effects of disease related fatigue, during the short evaluation at the end of the testing.

Discussion

Although the majority of MS studies report impairments of attention to be very frequent, this particular cognitive dysfunction is not very well described in the literature of MS. One important reason for this failure of research is probably the major methodological difficulties inherent in the experimental study of attention. It is difficult to operationalise the specific aspects of attention in behaviour. Even in the very simple model of attention which forms the basis of this review, it is difficult to categorise tests within the subtypes of attention.

Based on the studies with the Stroop test and cancellation tasks, the evidence points relatively unequivocally to a deficit in focused attention or response suppression. Nevertheless, there is a need for more knowledge about this deficit, which possibly should be based on evidence from other types of tasks. Likewise there is a relatively clear tendency towards impairment in tests of divided attention, often measured by slowed information processing. MS is a disease that affects the myelin, and it is therefore not surprising to find impairments in rapid processing of information to be very frequent. It is interesting to note the lack of relation between reduced speed of information processing and illness variables, as for example disease duration, course of disease and age, reported in some of the studies. This indicates that attentional dysfunction might be rather specific in nature, and sometimes independent of the general cognitive decline. In most tests of attention, motor function and general cognitive ability plays an important role for the results. In these cases only groups of patients matched on motor and cognitive performance should be used, to prevent the influence of these variables. Fatigue is a very frequent subjective experience of MS patients, and a few studies using vigilance tests indicate that, even in some MS patients with mild cognitive deterioration, the ability to maintain a stable level of attention is deficient.

Based on this review the overall conclusions are:

- Impairments in focused and divided attention are frequent in MS.
- Some experimental studies of sustained attention indicate that MS patients exhibit difficulties in maintaining a stable level of attentive responsiveness, even in shorter periods (15-30 minutes). A subjective and effort related experience of fatigue is common in MS.
- Deficits in information processing might be present in patients with mild physical handicap and/or no general cognitive decline.
- There is a need for a better understanding of the difficulties at different stages of information processing.

3.2.3 Executive functions

In spite of the great efforts in evaluating and describing executive functions, there are still areas of uncharted land within this field. Theories of executive functions are often described in terms from everyday language which are difficult to operationalize. This is also reflected in the numerous labels used for these functions - planning, problem solving, abstraction, thinking, reasoning, concept formation, "frontal lobe function", etc. The executive functions are individual cognitive processes, which are complex and highly interactive. The study of these functions is characterised by several methodological difficulties[180].

The prefrontal cortex is traditionally considered to be closely linked to executive functions. The prefrontal cortex is the brain region that most readily distinguishes a human brain from that of the other primates, but we still lack a complete understanding of its role in human behaviour (e.g. [179]). The frontal lobes play an important role in the initiation, regulation, and inhibition of human behaviour, but this is not to say that the executive functions are located solely in this part of the brain. The function of the executive systems is based on interaction with almost all other parts of the brain, both cortical and subcortical. Damage outside the frontal lobe may therefore cause dysexecutive symptoms as well.

The concept of executive functions is highly influenced by the theories of the Russian neurologist Luria [101], but others have contributed as well (e.g. [120,136,184]). In a recent paper Stuss et al. [180] suggested a new approach to the study of frontal lobe functioning. This approach combines knowledge and ideas from experimental neuroscience, lesion studies, and cognitive neuropsychology. This theory is briefly described and used as a framework for the description of executive functions in MS patients.

It is basically assumed that there is no single frontal (executive) process. Superimposed on the Cognitive System is the Supervisory System (SS), which functions by top-down activation or inhibition of more or less automatic subsystems (schemata) at lower levels in the hierarchy. The SS can be fractionated into component processes - energizing schemata (E), inhibiting schemata (I), adjusting automatic lower level selection (A), monitoring activity (M), and logical processing (L). The utility of the approach is illustrated by the example of attention.

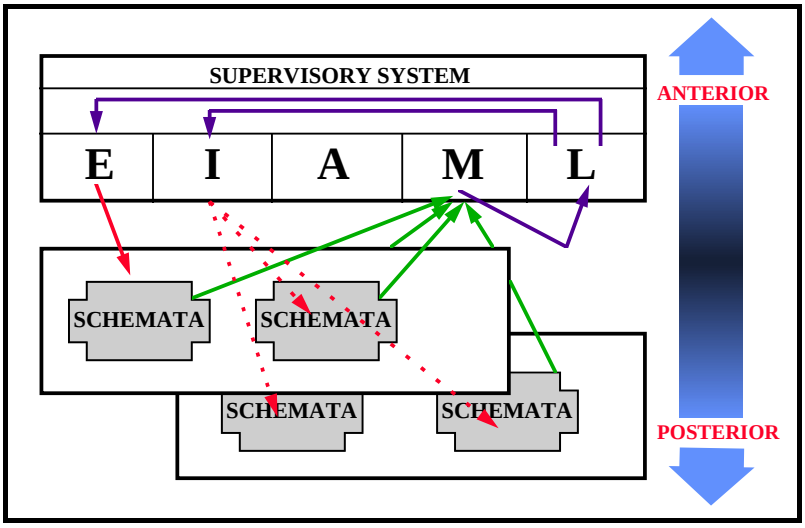

Figure 3.3. Model of the executive function of sustained attention.

To illustrate the theory imagine the situation when a radar operator is watching the flight traffic on a radar screen. He has to sustain attention and sustaining attention can, at the executive level, be described as the co-ordination of several simultaneously ongoing subprocesses. The relevant cognitive systems for this task have to be energized (solid red arrow), while other systems are inhibited in order not to disturb the ongoing activity (broken red arrows). Simultaneously the status of the entire cognitive system is monitored on-line (green arrows). At the logical processor, using information from the monitor processes, a continuous flow of questions are asked and answered about the relevance of the ongoing activity. This state in the cognitive system is maintained for a while, but an auditory stimulus (e.g. a little "bib" break signal) might alter the status radically. Through the monitoring of auditory schemata the SS becomes aware of the signal, and this will probably lead the logic operator to reason - "**if** break, **then** end of sustaining attention."

The model offers a relatively simple framework for demonstrating two basic problems. Firstly symptoms of impaired executive functions might be caused by deficits at the schemata level, deficits at the SS level, or both. In a disseminated disease like MS the cause of dysexecutive symptoms will often be a combination of localised anterior/posterior lesions and decreased informational flow due to impaired conduction. Secondly the model assumes that executive functions can be fractionated into a number of component processes. However, neuropsychological tests, believed to be sensitive to executive dysfunction, are not specifically designed to evaluate these functions (except the Tower of London test[165]). They

are generally complex tests, involving a number of cognitive skills which may be difficult to control for. This makes interpretation of test results ambiguous.

Rao[140] reviewed the literature of executive functions in MS under the headline of conceptual/abstract thinking. The majority of studies used the Halstead Category Test (HCT)[64]. Four MS studies reported no group differences compared to other brain damaged patients. Another four studies found MS patients impaired, but in one study only patients with chronic progressive MS was impaired and not patients with relapsing remitting MS. The Halstead Category Test yields only a single summary score, which tells little of the underlying cognitive deficits. Only one study used the Wisconsin Card Sorting Test (WCST)[67] and found both chronic progressive and relapsing remitting MS patients impaired on this test compared to normal subjects. One study reported MS patients to be impaired in the Weigl Sorting Test[189]. Several studies revealed a tendency of perseveration. Rao concluded that cognitive reasoning skills were frequently reported to be impaired in MS patients. The exact nature of this cognitive disturbance was not very well described and there appeared to be considerable interpatient variability in the range of these cognitive deficits.

Since this review in 1986 a number of studies have examined executive functions in MS. HCT was used in three studies which found MS patients to be unimpaired compared to normal controls[51,78,82]. Rao et al.[142] found MS patients to be impaired on the Booklet Category Test[38] compared to healthy controls, whereas the study by Krupp et al.[88] only found a tendency towards impairment ($p<0.09$). In the only study of Weigl's Sorting Test it was reported that only 9.5% of 42 MS patients were impaired in comparison with a group of healthy controls. A great number of studies used WCST. Patients performed significantly below normal controls on one or more measures of WCST (e.g. total number of errors, perseverations, categories) [13,15,19,20,32,47,108,116,142,155,183,185], and only three studies reported unimpaired performance[51,78,186]. Some of the studies used the Milner [114] administration and in other studies the modified administration by Nelson[121] was used.

Two other tests not included in the review by Rao[140] is the Controlled Oral Word Association Test (COWAT)[24] and Raven Progressive Matrices (RPM)[147], which also depend on intact executive functions. In three studies RPM performance by MS patients was significantly

lower than that of healthy controls[3,53,142]. Amato et al.[3] found the impairment to be present even in the early phase of MS (mean disease duration 1,6 years). In Comi et al.[32] 47% of secondary progressive MS patients (n = 17) performed below the normal range on RMP, whereas all patients with primary progressive MS (n = 14) surprisingly fell within the normal range. Filippi et al.[47] found 9.5% and Jennekens-Schinkel et al.[78] no MS patients impaired on RPM compared to healthy subjects. COWAT was used in a great number of studies and all studies, except Franklin et al.[54], found impaired performance in MS patients compared to normal controls[13,15,19,20,51,53,82,88,108,116,142,183].

In a recent study of executive functions in MS Foong et al.[53] tested 42 patients with a computerised version of the Tower of London test, developed by Shallice[165] to be sensitive to impairment in executive functions. The patients were compared to 40 healthy controls on measures of motor initiation and execution times, initial and subsequent thinking times, number of problems solved, and number of moves. MS patients used significantly longer initiation and execution time, more moves to solve a problem, and solved fewer problems. Initial and subsequent thinking times did not differ from controls. In addition MS patients were impaired on the Cognitive Estimation Test[167], Stroop[178], The Corsi Block Tapping Task[115], plus the two tests mentioned above COWAT and RPM. From an analysis of the neuropsychological data and MRI lesions, it was concluded that the contribution of frontal lobe pathology to this aspect of cognitive impairment is difficult to delineate and probably less significant than previously reported. Intra individual analyses indicated that some aspects of executive function may fractionate and can be more severely affected than others in the same individual.

Only a few studies report specific correlations between the executive functions and disease variables. Some studies observed significant associations between some of the tests mentioned above and disease variables (eg. EDSS, disease duration, depression) [3,15,108], whereas other studies did not [53,78]. Taken together no obvious relationship between executive function and disease variables in MS seem to exist.

The studies reviewed above show that MS patients often are impaired in tests, which put more or less demands on executive functions. In almost all studies of WCST MS patients

performed below controls, but the exact nature of this deficit is not clear. Little is known about the specific task demands in for example WCST. Using the model of Stuss et al.[180] perseveration in WCST might be caused by dysfunction in component processes of inhibiting schemata (I) or poor monitoring (M). Difficulties of defining the sorting criteria might be a failure of the logic processor (L). Low production of words in COWAT could be caused by a general disability to energize schematas. In addition, widespread brain damage in regions communicating with SS may result in some of the same symptoms. The study by Stuss et al points in the right direction, tending to clarify the basic cognitive nature of executive functions. However future studies should try to explain the concepts of for example "logic processor" more in detail.

Based on this review it can be concluded that:

- In the majority of studies MS patients were impaired in neuropsychological tests of executive functions compared to healthy controls, though a number of exceptions exist.
- Symptoms of executive dysfunction may be caused by localised brain damage in anterior parts of the brain, by more widespread pathology, or both.
- There is no firm association between general disease variables and executive function.
- Future studies need to be more explicit about the basic component processes involved in executive functions.

3.2.4 Language

Human language is a complex interactive process involving sensory integration, symbolic association, the use of learned syntactic patterns, verbal memory and motor skills. Aphasia is one of the classical neurological disturbances which is rarely associated with MS, and linguistic functions have not been extensively studied in MS.

Accordingly the comprehensive review by Rao [140] found only one paper on aphasic disturbances in MS. In this paper Olmos-Lau et al. [124] suggested that paraphasic disturbances occurred rarely in MS, and if seen, resulted from demyelinating lesions extending into the grey matter of the dominant hemisphere. They reported a case of "motor" aphasia in a 17-year-old woman and 14 other published case reports of aphasia in MS. The earlier case reports were criticised for their brief and poorly documented clinical descriptions, and only four papers reported pathological confirmation of MS. A later review of cognitive and emotional disturbances in MS by Beatty [11] reached almost the same conclusions about language function. Disturbances of speech production (such as hypophonia and dysarthria) are common, but aphasia, alexia and agraphia are rare.

In 1992 Achiron et al. [1] published two cases of aphasia in relapsing-remitting MS. Both patients presented with acute onset of non-fluent aphasia. MRI demonstrated unusually large plaques (about 5 cm in diameter) in the frontotemporal region of the dominant hemisphere. It is speculated why aphasia is so uncommon in MS since demyelinating lesions in frontotemporal areas are common. It was suggested by Achiron that only white matter plaques that are sufficiently large to simultaneously involve and disrupt commissural, association, and projection fibers in the dominant frontotemporal region can cause motor aphasia.

Some studies published since 1986, although not primarily concerned with language function, add a bit more evidence to the picture of language function in MS. In a number of studies the Token Test and other tests of comprehension revealed no impairment in MS patients [5,32,33,47,50,54,142]. Pia Amato et al. [3] examined a sample of 50 MS patients with low disease duration. At the initial test the patients did not differ from a healthy control group on the Token Test, but at retesting four years later their performance was significantly below controls. Results from studies using the Boston Naming Test, and other tests of naming

pictures or objects, do not indicate severe difficulties in naming [15,54,74,116,142,155,183,186]. In Beatty et al. [20] MS patients (n = 103) performed significantly below normal controls, but a large proportion of the patients received medication affecting CNS function (antidepressants, corticosteroids, benzodiazepines, opioid painkillers), and the control group was small (n = 32).

Klonoff et al. [82] found normal sentence repetition in 86 MS patients with relatively mild disease progression. A few studies have reported unimpaired writing [74,123] and spelling [51]. In two studies by Jennekens-Schinkel et al. [74,75] MS patients and healthy controls comitted an equally low percentage of reading errors, but in one study the MS patients read at a slower speed [75]. Similarly, Van Dijk et al. [186] reported that reading aloud was slower in MS patients than in controls, but types and number of errors revealed no differences between the two groups. Finally, a recent study by Kujala et al. [91] found impaired language functions, even in a group of MS patients with mild cognitive deterioration, compared to healthy controls and a group of cognitively preserved MS patients. The mildly deteriorated MS patients were impaired in naming, reading, and writing to dictation. Furthermore, the mildly deteriorated MS patients were generally slower than both the healthy controls and cognitively preserved MS patients.

In conclusion, this short review of language functions in MS support the clinical impression that:

- Cases of severe aphasia exists, but they are rare in MS.
- Neuropsychological test results indicate that language comprehension and naming abilities are unimpaired in most patients.
- A few studies of writing, spelling and reading indicate that these functions tend to be qualitatively unaffected, but that speed of reading is slower in MS patients.

3.2.5. Visuospatial Functions

In the comprehensive review by Rao [140], no references were reviewed under the heading of visuoperceptive, visuospatial, or visuoconstructive disorders in MS. In a recent review of cognitive disturbances in MS [11], the only study of visual processing tasks mentioned is Rao et al. [142]. This is a reflection of the very limited evidence about visuoperceptual and spatial functions in MS. It seems strange that the knowledge of visuoperceptual functioning is so limited in a disease which is known to commonly involve the visual system. However, a closer look at the MS literature reveals a little more evidence about visuospatial functions.

A number of studies examined basic visuoperceptual functions in MS patients. Recognition of motion-defined shapes seemed to be deficient [149], but not chromatic or achromatic vision [158]. Snellen acuity was spared in a sample of 25 MS patients [149]. In two studies performance on the Benton Facial Recognition Test [25] was impaired [15,142]. Two other Benton tests, the Visual Form Discrimination Test and Judgement of Line Orientation Test (JLOT), were found to be impaired in a study by Rao et al. [142], but in the study of Beatty et al. [20] JLOT was unimpaired. The JLOT was also used in three studies which found that between 20 and 30% of MS patients were impaired [32,33,47]. Filley et al. [51] reported normal performance in MS patients judging spatial relations. In two studies performance in Hooper Visual Organization Test [70] was unimpaired [116,142] and in a third study [183] 45% of the MS group fell below “established cut-off scores” from normative groups for this test.

The copying of the Rey Complex Figure [97] was impaired in a study of Franklin et al. [54], but other studies revealed normal performance in copying more simple drawings [3,74,75]. Analysis of the drawings revealed striking problems with pencil strokes in the MS group, most likely related to motor, sensory and/or coordination problems [74,75]. Construction of WAIS Block Designs was normal in two studies [82,157], but a third study revealed abnormal performance in this test [89].

Most of the studies reviewed above are not primarily concerned with visuospatial functioning in MS. This is a major problem, because questions of visuospatial function in MS are very complicated and require specific tailor made study designs. A major obstacle to this kind of

research is the presence of, and interaction between, deficits at the level of primary visual pathways and deficits at a higher level of visuospatial processing.

In conclusion, knowledge about visuospatial function in MS is very limited and evidence from the few studies reviewed here does not bring about a general clarification of the topic. The studies indicate that both basic visuoperceptual and/or spatial functions may be significantly impaired in MS, but the frequencies of these impairments remains unclear.

4. PRESENTATION OF THE MS STUDY

4.1 Introduction

In this section, methods and results from a large population based MS study are presented. Denmark has a long tradition for careful registration of the Danish population. These population based registers often form a unique opportunity to study social and epidemiological topics in detail. Using the Danish MS Registry makes it possible to define cohorts of MS patients which are very close to the "true MS population". The study described here took place at the National University Hospital Rigshospitalet in Copenhagen, between May 1993 and May 1995, and was part of a large MS project. The aim of the project was: 1) to describe correlations of clinical disability and cognitive findings to brain Magnetic Resonance Imaging (MRI) in MS [163] and 2) to describe frequency and pattern of cognitive dysfunction in a population-based population. The first part was performed by Karen Schreiber, MD and the second part of the study is presented below. Both studies are based on the same candidate population of MS patients.

4.2 Methods and random selection

4.2.1 The candidate population

The Danish MS Registry (DMSR) is a national register based upon the Danish population of about 5 million people[86]. It was founded in 1956 following a nation-wide prevalence survey of MS, and incident cases have been continuously registered since 1948. The completeness of the DMSR has been estimated to be about 90%, and the validity is approximately 94% at post mortem follow-up [86]. Cases in the DMSR are classified according to the diagnostic criteria of Allison and Millar[2] and further modified to include laboratory (IgG-index and oligoclonal bands) and paraclinical (evoked potentials) data (Appendix II) [86]. This diagnostic classification includes 4 MS categories: clinically definite, probable, latent and observational cases.

Approval by the Ethical Committee (jr.nr. KF 01-176/93) and the registration authorities was obtained. The DMSR was revised in 1992, and the candidates for this study were drawn from the register in April 1993, according to the following four criteria:

1. The geographical study area was defined as the region of northern Zealand including the county and the city of Copenhagen, Frederiksberg, the county of Frederiksborg as far as the city Hillerød, and the county of Roskilde as far south as the city of Køge; thus excluding only some of the smaller communities. This area represents a predominantly urban population of about 2 million people.

2. The study candidates were defined according to their age of 35-49 years and divided into 3 age-cohorts: 35-39 years(born 1954-58), 40-44 years (born 1949-53) and 45-49 years (born 1944-48). An upper limit at 50 years of age was used because the study population primarily was designed for a parallel study (conducted by Karen Schreiber, MD) of correlations between MRI and various disease variables. Using people older than 50 years in such a study would have introduced serious difficulties in the discrimination between age related changes and MS related changes in white matter.

3. They were drawn according to a disease duration of 5 to 19 years, and divided into 3 groups: disease duration of 5-9 years (onset of symptoms 1984-88), disease duration of 10-14 years (onset of symptoms 1979-83) and disease duration of 15-19 years (onset of symptoms 1974-78).

4. Furthermore, they were drawn according to the diagnostic criteria mentioned, including observational and deceased cases. The deceased cases were taken into account in order to avoid a potential bias of sampling a selected subgroup of the total population, namely those who had survived up to the day of examination.

302 candidates fulfilled the diagnostic criteria mentioned above and this group was divided into 9 strata according to age and disease duration (table 4.2.1). Another 108 were observational candidates. The diagnostic classifications of these candidates were revised by Karen Schreiber, MD, to ensure completeness of the candidate population. An important aim of the revision was to ensure that possibly mild or benign MS candidates not be overlooked. Therefore, the discharge letters and medical records in the DMSR were scrutinised, in order to evaluate the possibility that candidates had developed new symptoms after the latest

available information. In about half of the observational cases the initial symptoms were characteristic of MS, and letters were sent to general practitioners who answered questions about new symptoms or gave information that could be used to verify the diagnosis.

Table 4.2.1 The candidate population

Onset/age	35-39 years	40-44 years	45-50 years	total
5-9 years	26	24	30	
10-14 years	35	33	42	
15-19 years	26	40	46	302
Observational candidates	33	26	49	108

In each age-cohort a number of the observational candidates were deemed either *suspected candidates* or *unsuspected candidates*. The suspected candidates who, after further information from the general practitioners, fulfilled the MS criteria were reclassified and included in the strata (table 4.2.2). A total of 24 were reclassified and 13 of these candidates were later randomly drawn into the study population.

Table 4.2.2 Revision of observational cases

Age-cohort	35-39 years	40-44 years	45-50 years	total
Observational candidates	33	26	49	108
Deemed unsuspected candidates	16	13	23	
Deemed suspected candidates	17	13	26	
Reclassified as MS candidate	9	6	9	24
(later randomly drawn to the study population)	6	3	4	

After this revision, the candidate population consisted of the 302 candidates plus the 24 reclassified candidates - in all 326 candidates, distributed in the 9 strata shown in table 4.2.3.

Table 4.2.3 Revised candidate population

Onset/age	35-39 years	40-44 years	45-50 years	total
5-9 years	29	26	32	87
10-14 years	38	35	46	119
15-19 years	29	42	49	120
Total	96	103	127	326

At the time of the latest revision of the DMSR (1992), 23 cases had died and a further 9 cases died after being drawn to the study. For this reason 32 candidates were not eligible for the study. In table 4.2.4 the distribution of the surviving candidates are mapped together with the surviving proportion in percentages of the original onset cohorts. The survival proportion was 89.4% (270/302). The 24 observational candidates reclassified as MS candidates were not included in this analysis, but they were all alive and equally distributed across strata. The evenly balanced proportion of survivors and the small number of dead cases do not indicate any significant differences between strata.

Table 4.2.4 Distribution of the surviving proportion of the original onset cohorts

Disease duration	35-39 years	40-44 years	45-50 years
5-9 years	25 (96%)	22 (92%)	27 (90%)
10-14 years	33 (94%)	30 (91%)	39 (93%)
15-19 years	20 (77%)	35 (88%)	39 (85%)

4.2.2 Cases eligible for the MS study population

In the study by MD Karen Schreiber[163], in order to make valid statistical evaluations, it was a prerequisite that cases were almost equally distributed regarding age and onset cohorts. To ensure this balanced representation, study candidates were drawn by random selection from each stratum by lots. This randomisation was planned to continue until candidates in the study population were nearly equally distributed in the nine strata. The study population is therefore not a cross-sectional sample of the true MS population.

A total of 164 cases were drawn from the revised candidate population. Before the patient was approached, the general practitioner was notified in order to avoid confronting patients without knowledge of their diagnosis. Then the patient was sent an informative letter and contacted by telephone if possible. The patients who accepted to participate were interviewed and had a neurological examination by MD Karen Schreiber (KS), either at the patient's home or at the department. At this first visit KS informed about the neuropsychological part of the study and made an appointment for the neuropsychological examination if the patient accepted to participate.

The final study population was found according to the following inclusion and exclusion criteria:

Inclusion:

Patients who were: 1) drawn at random from the revised candidate population and 2) who, after the neurological examination, had a diagnosis of definite or probable MS according to the Poser criteria[132].

Exclusion

1. Death (9 cases)
2. Patients who had MS, but had moved out of the area (3 cases)
3. Patients, for whom the neurological examination revealed that they did not fulfil the Poser criteria for definite or probable MS (false positive study candidates) (7 cases).
4) Patients who proved not to have MS (7 cases) - the alternative diagnoses were: encephalitis sequelae, hereditary ataxia, epilepsy (x2), herniated lumbar disc, systemic lupus erythematosus and syringobulbia.
5) Four MS patients who had other organic disease, which might interfere with the performance in the neuropsychological examination (e.g. hydrocephalus) (4 cases)
6) Previous or current episodes of major depression (3 cases)
7) Moderate or severe head trauma (post traumatic amnesia (PTA) > 1 hour) (4 cases)
8) Alcohol or drug abuse (2 cases who were, however, also excluded for other reasons)

After the exclusion of 37 patients, 127 candidates were eligible for the MS study population (table 4.2.5). 19 of these candidates did not want to participate in the study at all, and 9 candidates refused to have a neuropsychological examination (in all 28 non-responders). Thus 99 patients were included in the neuropsychological study population. Table 4.2.6 shows that the balanced distribution was achieved for the age cohorts, but not for the disease duration cohorts. There was an excess of patients with long disease duration, whereas patients with short disease duration were underrepresented.

Table 4.2.5 General flow chart of candidates

Study candidates revised		326
Random stratified selection of candidates		164
Candidates excluded due to:		
Death	9	
Moved outside study area	3	
Possible or observational MS	7	
Other organic disease than MS	7	
MS and other CNS disease that might affect the neuropsycholo-gical tests	4	
Episodes of major depression	3	
Head trauma (PTA > 1 hour)	4	
Drug or alcohol abuse	(2)	-37
Eligible for the MS study population		127
Non-responders		-28
MS study population		**99**

Table 4.2.6 Distribution of the study population

AGE/ DISEASE DURATION	35-39 years	40-44 years	45-50 years	Total
5-9 years	6	8	8	22
10-14 years	13	8	11	32
15-19 years	13	16	16	45
Total	32	32	35	

4.2.3 The non-responders

28 of the 127 MS patients eligible for the study (22%) refused to participate in the study. Machintosh-Michaelis[108] is the only neuropsychological MS study which have a comparable study design, and here 17,9 % refused to participate. Clinical data of the non-responders available in the DMSR made it possible to compare this group with the population eligible for the MS study (table 4.2.7).

Age and disease duration were calculated to the year of 1993 for both groups. The sex ratio was the same and showed the normal preponderance of female patients. Age at MS onset, disease duration and age at assessment revealed no significant differences between groups. The median Kurtzke Disability Status Score (DSS) was not significantly different in the two samples. The distribution of severity between the population of eligible MS patients and non-responders shows differences of approximately 10% in the moderate and severe groups. This means, not surprisingly, that a few more of the most disabled patients refused to participate. In spite of this small difference the study population may be regarded as representative of the eligible MS population.

Table 4.2.7 Clinical data on the population eligible for the MS study and the non-responders

	The study population (n = 99)	**Non-responders (n = 28)**	**p**
Female/male ratio	1,7	1,5	
Age at MS onset			
Mean	28,6	28,5	0,93[a]
Range	16-43	16-40	
Disease duration			
Mean	13,6	13,4	0,66[a]
Range	5-24	0-35	
Age at assessment			
Mean	42,2	41,0	0,23[a]
Range	35-49	36-49	
DSS			
Median	4	5	0,26[a]
Range	1-8	1-9	
Severity			
Mild (DSS 0-2)	35 (35,4%)	10 (35,7%)	
Moderate (DSS 3-5)	35 (35,4%)	7 (25,0%)	
Severe (DSS 6-9)	29 (29,2%)	11 (39,3 %)	

[a] Mann-Whitney U Test

4.2.4 The study population

The 99 MS patients in the study population can be described according to some general patient characteristics and measures of the severity of impairment. The study population consisted of 62 females and 37 males (ratio 1,7:1). The mean age at assessment was 42,9 years (range 35-50). The mean age of onset was 30,3 years (range 18-42), and almost even for females (30,0 years, range 21-42) and males (30,7 years, range 18-41). The mean duration of disease was 12,6 years (range 4-22) and this was also even for females (12,7 years, range 5-20) and males (12,4 years, range 4-22).

With one exception all patients were examined during a clinically stable period (one patient had an attack in the spinal cord between the medical and the neuropsychological examination). 9% received medicine for pain, 9% antidepressants (without sedative effects), 7% hypnotics, 2% psychoactive drugs, and 29% antispastic drugs.

The disease course was defined according to the criteria described in McAlpine[106]:
1) Relapsing/remitting: A history of relapses and remissions (complete or incomplete) without gradual deterioration (27% of the study population). In 10 MS patients with RR (10% of the study population) the disease was defined as benign (duration of at least 10 years and a maximal EDSS of 3).
2) Secondary progressive: After an initial relapsing/remitting course, progressive deterioration had evolved at some time during the illness for at least 6 months, with or without superimposed relapses (54% of the study population).
3) Primary progressive: Progressive deterioration from onset, without evidence of relapses and remissions (19% of the study population).

The severity of the impairment in the study population was measured by EDSS [93]. The mean EDSS was 5,6 (SD = 2,23, range 1-9.5, median 6). Table 4.2.8 shows the distribution of neurologic impairment according to the conventional grouping of EDSS scores in mild, moderate, and severe impairment. Although it is not evident from table 4.2.8 the distribution of EDSS scores (figure 4.2.1) tends towards a bimodal distribution, which is known from other studies too [112,190].

Table 4.2.8 Distribution of neurologic impairment according to EDSS

	MS patients	Percentage
Mild (EDSS 0-3)	19	19,2%
Moderate (EDSS 3.5-5.5)	24	24,2%
Severe (EDSS 6-9.5)	56	56,6%

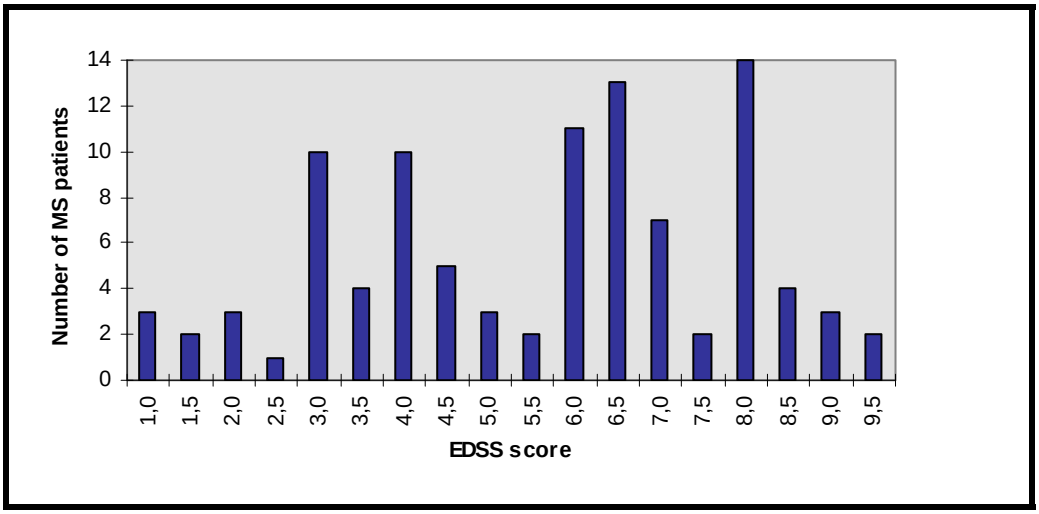

Figure 4.2.1: Distribution of EDSS scores in the study population

4.2.5 The neuropsychological examination

The neuropsychological examination took place as soon as possible after the neurological examination. The majority of the examinations were performed at the Neurological Department, and only about 10 of the examinations were performed outside the hospital (patient's home or nursing homes). Patients' transport to the hospital was arranged and paid for. Before the beginning of the neuropsychological examination all patients had a short interview about their health since the neurological examination and about school, education, and work. The test session was scheduled to last 3 - 5 hours, and patients were offered a break any time they wanted during the day.

MS patients are a very heterogeneous group. It was not possible to compose a test battery that could be completed by all patients and still have a high sensitivity for cognitive dysfunction. The study population was therefore divided into three groups according to the patients' ability to co-operate during the neuropsychological examination (table 4.2.9). All neuropsychological examinations were performed by the author, except 11 MS3 examinations which were performed by a college, neuropsychologist Karin Nørgaard, during a period when the author was occupied by other work.

Table 4.2.9 Groups of patients in the study population

Group	MS Groups
MS1 (n = 6)	Patients who were not able to perform neuropsychological testing due to their mental and/or physical condition. Some patients could not co-operate reliably in a short mental status examination (MSE). Some patients were so disabled that testing was not attempted. Two patients were placed in this group, because they refused to continue after a few MSE tests.
MS2 (n = 11)	Patients were able to complete a short mental status examination, but could not complete the more demanding test battery.
MS3 (n = 82)	Patients were able to complete most of the test battery of 17 neuropsychological tests.

The patients in MS2 were tested with 13 tests of a brief Mental Status Examination (MSE) from University Hospital Rigshospitalet in Copenhagen described in table 4.2.10.

Table 4.2.10 Tests from Mental Status Examination (MS2 group)

Test	Description
Orientation	Time, place and the patient's own data.
Information	Seven simple questions (e.g. the name of the queen's husband?)
Three Words	The patient is told three words, to be recalled after 10 and 30 minutes.
Three Objects	Three objects are hidden, and the patient is asked to recall the objects and locations after 10 and 30 minutes.
Calculation	Eight arithmetical problems.
Digit Span Forward	Maximum digit span forward.
Verbal repetition	Repetition of ten sentences of different length.
Verbal abstraction	The patient is asked to explain four proverbs and find the super ordinates in a short four item Similarities Test.
Naming Test	Naming pictures of 30 well-known objects (car, dog, orange, etc.)..
Classification	Patients are asked to classify groups of five pictures from the Naming Test
Free Recall	Free recall of the pictures in the Naming Test after a short delay of a few minutes.
Recognition test	Patients have to identify 12 pictures from the Naming Test, mixed up with 12 pictures they have not seen.
Verbal Fluency	Number of animals mobilised in one minute.

The 82 patients in MS3 were examined with a more extended test battery (TB) described in table 4.2.11. The tests in this battery were chosen to make a cognitive profile of the MS3 patients possible according to the five classic cognitive domains reviewed in section 3 of this

thesis (memory, attention, executive functions, language, visuospatial functions) and verbal intelligence.

Table 4.2.11 Test Battery (MS3 group)

Tests	Comment
WAIS Vocabulary[188]	Split half version (odd numbered tasks). The split-half result was multiplied by 2.
WAIS Information[188]	
Street Gestalt Completion Test [56]*	Identification of 20 fragmented pictures.
Rey's Complex Figure[97]	Copying and free recall after 3 minutes. Scored as described by Lezak.
Boston Naming [81]*	Split half version (odd numbered tasks).
Naming Famous Faces *	Identification and naming of 20 pictures showing the head of famous persons known by most Danes.
Proverbs	Danish multiple choice Proverb Test (10 items), which requires the patient to choose among five different statements the one implying the same meaning as the target proverb (a.m. Öberg).
Verbal fluency *	Animals and words with S, within 1 minute.
Digit span [175]*	The Spreen & Benson NCCEA version. Forwards and backwards.
List Learning [30]*	A.m. Buschke (selective reminding, 10 words).
Raven Advanced [147]	12 items, section A.
Design Fluency [150]	A.m. Regard - the test requires the person to draw as many different designs as possible in three minutes, connecting five dots in different ways.
Mental Arithmetic [96]*	10 arithmetic tasks, which have to be calculated within 20 seconds each.
Tower of London [165]	A.m. Shallice. - non-computerised version.
Auditory Motor Attention *	Simple test demanding the patient to knock at the table each time the letter A is mentioned, from a list of 75 random letters read by the examiner.
Stroop(modified version) [178]*	This version consists of 50 cards with either coloured crosses(10) or coloured colour names (40 - interference part).
Symbol Digit Modalities Test [172]	A.m. Smith. - A key combining nine pairs of digits and symbols is presented on a sheet. Below the key, the nine symbols are presented in rows in random order, and the task is fill in as many as possible of the corresponding numbers in 90 seconds.

*** Tests used in the dementia index.**

Neurological disability and disease severity were measured by the Expanded Disability Status Scale (EDSS) [93], Ambulation Index (AI)[66], Incapacity Status Scale (ISS) [171] and Neurologic Rating Scale (NRS) [170]. The four rating scales are described in more detail in appendix I. Furthermore all patients had a Mini Mental Status Examination (MMSE) [52]. Mood disturbances were assessed only in the MS3 group, using the State-Trait Anxiety Inventory

(STAI) [174], Beck Depression Inventory (BDI) [22], and Hamilton Depression Scale (HDS) [65]. STAI and BDI were completed at the neuropsychological examination. HDS, and the neurological rating scales (EDSS, AI, NRS, and MMSE) were scored by KS at the initial examination before the neuropsychological examination (test interval mean 29,6 days (range 0-124)). Although on average one month passed between the examinations, only one patient reported marked changes in mood since the neurological examination.

Due to an unfortunate error in the majority of the BDI photo copies, most patients did not answer the five questions on the last page, concerning fatigue, loss of appetite, weight loss, somatic preoccupation and sexuality. These five questions are no doubt important in relation to depression, but it was decided to include the BDI data for a number reasons. Firstly the questions in BDI have a very high intercorrelation. A study of 262 patients with cancer revealed a correlation of $r = 0,95$ ($p < 0,001$) between the full BDI and the abbreviated form used here (BDI-abbr.) (Hans Henrik Jensen & Erik Lykke Mortensen, personal communication). Secondly there was a significant correlation between BDI-abbr. and HDS ($r = 0.66$, $p < 0.001$). Finally it may be argued that the symptoms in these particular questions may be difficult to differentiate from primary MS related symptoms (e.g. fatigability, decrease in libido, weight loss). For these reasons it was decided to use data from the BDI-abbr. form in the study.

Test completion codes: Patients with MS form a heterogeneous group, with a very wide spectrum of disabilities. This factor plays an important role, especially in large scale studies like this with tight time schedules. In order to get some information about the reason for missing data, a system of test completion codes was used.

Table 4.2.12 Test completion codes

Completion Codes	
CC1	The test could not be completed reliably, due to motor and sensory disability.
CC2	The test could not be completed reliably due to poor reading abilities.
CC3	The test could not be completed reliably due to visuospatial disability.

CC4	The test had to be discontinued, due to poor co-operation other than 1,2,3 (e.g. poor concentration, fatigue or lack of time).
CC5	The test was not completed, but could presumably be completed under optimal circumstances.

After each examination a test completion code was assigned for missing test scores (table 4.2.12). The code tells: 1) why a test had to be discarded (code CC1-CC4) **and** 2) whether the examiner judged that the test probably could be passed under optimal conditions (code CC5).

4.2.6 Control groups

Control group I: The 75 normal healthy controls for the MS3 tests were recruited partly for use in this study and partly as a general Danish standardisation of neuropsychological tests. The work with the control group was severely delayed, due to a long delay in the permission from the Danish Ethical Committee to collect these control data and due to difficulties in the recruitment of healthy control persons. Control subjects were examined by two neuropsychologists Irene Mortensen and Lisbet Marstrand. Fifteen of the control subjects were close relatives to MS patients attending the MS Clinic at Rigshospitalet. The remaining controls were recruited among friends of the MS relatives, employees at a nursing home for the elderly, a primary health care centre, and by informal contacts. All controls were unpaid and volunteered for the two hours of neuropsychological testing. Control subjects were excluded if they had a history of neurological illness, psychiatric illness, alcohol or drug abuse, or any health related problem that might influence test performance.

The groups were compared on a number of background variables - age, female/male ratio, years of schooling, vocational training, and education index (school years + vocational training) (table 4.2.13). Vocational training was rated on a scale from 1 (none education) to 5 (university grade). Controls were younger and both years of schooling and education index were higher than in MS3 patients. There was no significant difference in vocational training between the groups.

Table 4.2.13 Background data

	MS3	**Control group I**	**P =***

Age	42,9 (4,5)	36,7 (12,2)	P < .001
Sex ratio	1,6	1,7	
Years of schooling	9,7 (1,5)	10,7 (1,4)	P < .001
Vocational training	3,1 (1,0)	2,8 (1,3)	NS
Education index	12,8 (2,3)	13,5 (2,1)	P < .05

*** Mann Whitney**

Control group II: The control group for the MS2 tests were part of larger control group previously published by Mortensen and Gade [119]. After completion of a basic test battery, the participants in control group II completed a battery of mental status tests (these data are not published). All subjects ≤ 57 years were included in the MS2 control group (n= 32) and the subjects had no history of neurological illness, psychiatric illness or alcohol/drug abuse. Though the controls were slightly older, Mann Whitney tests of age, years of schooling and vocational training revealed no significant differences between the MS2 group and controls (table 4.2.14).

Table 4.2.14 Background data of MS2 and Control group II

	MS2	**Control group II**	**P =***
Age	44,2 (3,4)	47,8 (8,2)	NS
Sex ratio (f/m)	2,6	1,9	
Years of schooling	8,9 (1,4)	8,5 (1,5)	NS
Vocational training	2,6 (1,0)	2,6 (1,0)	NS

*** Mann Whitney**

4.2.7 Data analysis

Mental status examination (MS2): Thirteen MSE test scores of memory, immediate span, calculation, naming, verbal abstraction, and verbal fluency were included in this analysis of the MS2 group (table 4.2.10). A previous study of Alzheimer patients included some of the same MSE tests [187]. In this study the raw scores were standardised using the mean and the standard deviation of control group II. However, this method is problematic in some of the tests, when the raw score distributions are highly skewed, and/or the variance is low (and the standard deviation consequently very small).

An exploratory analysis of the raw score distributions from 96 mental status examinations of normal subjects, performed in relation to the Mortensen and Gade [119] study, revealed that z

score transformation was highly problematic in 6 of the 13 MSE tests used in the MS2 group. It was therefore decided to subdivide the evaluation of the MS2 results in a binary scoring (6 tests) and z-score transformation (7 tests). Binary scoring of "passed" (0) or "failed" (1) was used for tests with a standard deviation of less than 1and a highly skewed distribution. For these tests a cut-off score classifying at least 90 % of the normal range was established (see table 4.2.15). In the remaining 7 tests raw scores were transformed to z scores using the mean and standard deviation from the subjects in Control group II.

Table 4.2.15 Tests of binary scoring

Control Group II TEST	Mean (SD)	"1" FAILED	"0" PASSED	PERCENTAGE OF THE CONTROLS CASSIFIED IN THE NORMAL RANGE
Orientation	13,9 (0,3)	≤ 12	≥ 13	100 %
Information	6,8 (0,4)	≤ 5	≥ 6	100 %
Three Words	5,9 (0,4)	≤ 5	6	91 %
Three Objects	12,0 (0,0)	≤ 11	12	100 %
Naming Test	29,7 (0,5)	≤ 28	≥ 29	97 %
Recognition Test	11,5 (0,7)	≤ 10	≥ 11	91 %

MS3 Test battery: A control group matching on age, years of schooling, vocational status and sex would be preferable, but this was unfortunately not possible for reasons described earlier. Regression analysis was therefore used in the comparison between MS patients and control group I and also provided an opportunity for characterising individual test performance.

- A preliminary analysis revealed that a simple standardisation (linear transformation) of the MS3 group, using mean and standard deviations of Control group I, resulted in extreme z-scores as low as -19,6. Raw scores were therefore normalised before the regression analysis. Normalisation of neuropsychological test scores generally results in standard score distributions closer to a normal distribution than does linear transformation [118].
- The single test scores from MS3 and controls were normalised, using the combined distribution in MS3 and control group I. The combined distributions were used because using only the control group to normalise test scores has the disadvantage that it is impossible to differentiate patient scores worse than the lowest score in the control group.
- The normalised single test scores were then standardised to a mean of 0 and a standard deviation of 1 in the control group (see [118]).

- Expected scores for each single test score were computed with age, age^2, sex and education index (school years + vocational training) as predictors based on a regression equation derived from the standardised scores of the normal controls[119]. Potentially vocational training could be affected by the onset of MS during vocational training and therefore not be appropriate as a regressor. Analyses revealed that 47 of the MS3 patients had onset of MS before the age of 30 years. The vocational level was seriously affected in only one of these patients, defined as a discrepancy of two or more scores between planned vocational training and achieved vocational status.
- Finally residual scores were computed as the difference between the observed z-score and the expected z-score. The residual scores therefore express the deviation from the normal mean in z-scores.

This kind of data analysis has been used in previous neuropsychological studies [55,57]. The analyses were performed with the Statistical Package for Social Sciences (SPSS) and Microsoft Excel.

Dementia index: The general cognitive dementia classification is based on the best possible information about the patients in the three subgroups. The information on the patients' cognitive abilities ranges from simple clinical rating scales in some cases to comprehensive neuropsychological testing in other cases. To examine the relationship between severity of dementia and other disease variables, it was necessary to combine the three different kinds of information into a common scale. Such a scale was not found in other studies and therefore a thirteen point dementia index (DI) was constructed for this study. The DI ranges from score 0 ("no cognitive impairment") to score 12 ("severe cognitive impairment")(see table 4.2.16).

Patients in the MS1 group could not co-operate in any kind of formal neuropsychological testing due to physical and /or cognitive impairment. Dementia for these 6 patients was therefore based on a single rating in the Incapacity Status Scale (ISS) [171]. The structured interview for the ISS was performed by MD Karen Schreiber (KS) as part of the standard examination (see appendix I). Only the score of "mentation" was used for the dementia rating. In this study the procedure was changed, and instead of the patient's own rating, the score reflects KS´s rating of the actual cognitive functional level based on careful questioning of the

patients and their relatives. The ISS is graded from 0-4. A score of 0 represents “normal function” and a score of 4 “total dependence on assistance from others due to cognitive dysfunction”. A score of 2 indicates that impaired cognitive function causes some restrictions in daily activities and this score is set as the cut-point of dementia in DI. Five of the MS1 patients were also briefly clinically evaluated by the author, who agreed in the ISS ratings by KS.

Dementia scoring of the MS2 tests was hampered by several problems due to test construction factors, described in the presentation of Control Group II. The scoring was therefore divided into a binary index and a z score index. In the binary index deterioration points (“1” = failed test) were simply summed. The deterioration point sum between 1 and 6 were then assigned a dementia score, according to the gradation described in table 14.2.16. For the remaining 7 MSE tests in the MS2 battery, dementia classification was based on linear z score transformation. An index z-score was calculated as the average of the 7 z-scores, and a DI score assigned due to the criteria described in table 4.2.16. Each step in the DI represent 1/3 average z score and a z score of -1,66 (theoretically corresponding to approximately 95% of the normal distribution) was chosen as the cut point between dementia and no dementia. The overall MS2 DI score was computed as the average of the binary DI score and the DI score assigned for the z index score.

In MS3 dementia was classified using the residual scores of 9 neuropsychological tests (see table 4.2.10). These tests were chosen because most patients were able to perform them, and because the tests were sensitive to a range of cognitive functions (i.e. attention, memory, executive function, language functions and visuoperceptual function).
A cognitive index was calculated as the average of the residuals of the nine tests. These cognitive index scores were restandardised to a mean of 0 and a standard deviation of 1, using the means and standard deviations of the control group. Finally conversion to DI scores was done in the same way as for the MS2 group.

Table 4.2.16 Dementia scale.

DEMENTIA	MS1	**x**			
	MS2		**x (MEAN) x**		

INDEX	MS3				x
	DI score	ISS	Binary (sum index)	MSE index (mean z-score)	Test battery index mean residuals
NO DEMENTIA	0	0	0	≥ -0,32	≥ -0,32
	1			-0,65 - -0,33	-0,65 - -0,33
	2		1	-0,99 - -0,66	-0,99 - -0,66
	3	1		-1,32 - -1,00	-1,32 - -1,00
	4		2	-1,65 - -1,33	-1,65 - -1,33
DEMENTIA	5			-1,99 - -1,66	-1,99 - -1,66
	6	2	3	-2,32 - -2,00	-2,32 - -2,00
	7			-2,65 - -2,33	-2,65 - -2,33
	8		4	-2,99 - -2,66	-2,99 - -2,66
	9	3		-3,32 - -3,00	-3,32 - -3,00
	10		5	-3,65 - -3,33	-3,65 - -3,33
	11			-3,99 - -3,66	-3,99 - -3,66
	12	4	6	≤ -4	≤ -4

Validation of the dementia index: An important question regarding this index method concerns the equivalencing of the DI scores derived from the different inputs (ISS, MSE and MS3 tests). How well does a dementia score computed from the MS2 test battery correspond to a dementia score derived from the MS3 tests, in the same patient? Preferably some of the MS3 patients additionally should have completed the MS2 test battery, but this was unfortunately not done in this study.

After the study period had finished, the author tested 11 neurological patients with both of the MS2 and MS3 test batteries. The patients were examined at the Neurological Department of the Western Zealand County Hospital in the city Slagelse. All patients were referred to a neuropsychological evaluation by neurologists. The patients were biased towards cases with differential diagnostic problems. The patients had diagnoses of MS, head injury, and dementia. The average age in this group (46 ± 16,3, range 18-67) was higher than for MS patients. Raw scores of the validation group were computed using the methods described under data analysis and dementia index. Afterwards binary index scores, z index scores, and residual index scores were converted to DI scores, according to the criteria described above (table 4.2.16). Table 4.2.17 shows the comparisons between MS2 DI scores and MS3 DI scores. The binary DI scores and the z DI scores were correlated at approximately the same level in both the validation group ($r = 0,70$; $p < 0.05$) and the MS2 group ($r = 0,68$; $p<0.05$).

Table 4.2.17 Comparison between MS2 and MS3 DI scores of the validation group.

TESTS	Mean (SD)	MS3 - DI score
MS2 - binary DI score	4,2 (2,8)	r = 0,83 (p < 0.01)[1)]
MS2 - z DI score	2,2 (2,0)	r = 0,80 (p < 0,01)[1)]
MS2 - DI score	**3,2 (2,2)**	**r = 0,88 (p < 0,001)[1)]**
MS3 - DI score	**4,0 (4,2)**	

1) Pearson correlations.

In conclusion, these data indicate a reasonable internal consistency in the criteria of dementia index scores across the MS2 and MS3 test batteries. The validation group is small and not comparable with the MS groups regarding age and aetiology, but despite this, DI scores independently derived from two different test batteries seems to end up at approximately the same level. The sample size is too small for a classification analysis.

4.3 Results

Differences between MS1/MS2 & MS3.

The patients in MS1 and MS2 were not able to perform comprehensive testing and differed significantly from MS3 in a number of neurological rating scales, but not in age, gender, education, and disease duration (table 4.3.1).

Table 4.3.1 MS1/2 compared with MS3

	MS1 & MS2	**MS3**	**Mann Whitney**
Age	42,8 (4,1)	42,9 (4,5)	NS
Sex (F/M ratio)	1,8	1,6	
School (years)	9,4 (1,5)	9,7 (1,5)	NS
Education	2,8 (1,1)	3,1 (1,0)	NS
Disease duration	12,3 (4,5)	12,6 (4,3)	NS
MMSE	18,1 (8,4)	29,0 (1,2)	P < 0.001
EDSS	8,3 (0,7)	5,0 (2,0)	P < 0.001
AI	8,6 (0,9)	4,0 (2,7)	P < 0.001
NRS	26,6 (13,8)	63,7 (17,7)	P < 0.001

Pattern of cognitive dysfunction in MS3

Table 4.3.2 presents the raw test scores, the normalised test scores, and the mean residual scores for the MS3 group. In the MS3 group, analysing residuals based on regression-equations obtained in the control group had two purposes: 1) To be able to compare the test results of the MS3 group and the control group unconfounded by any group differences with respect to sex, age, and educational level 2) To obtain a measure of intellectual impairment that was unaffected by the association between test results and sex, age, and educational level that can be observed in the control group. For example, in the MS3 group a relation between test results and age might reflect both “normal” age related impairments and age related disease progression. By using regression equations obtained in the control sample, only the variance associated with “normal” age related impairment are removed.

The regression coefficients obtained in the control sample are of course only sample statistics and not population parameters, and the mean residual in another sample of normal controls

Table 4.3.2 Results of cognitive testing

NEUROPSYCHOLOGICAL TESTS	N	Raw-scores	Normalised scores	Residuals	P =*
VERBAL INTELLIGENCE					
WAIS Vocabulary	82	60,0 (11,6)	0,17 (1,17)	0,10 (1,06)	NS
WAIS Information	81	20,8 (3,8)	0,09 (0,95)	0,08 (0,80)	NS
VISUOSPATIAL SKILLS					
Street Test (number correct)	79	12,5 (3,3)	-0,75 (0,94)	-0,72 (0,94)	< 0,001
Rey's Figure (copy)	67	34,2 (2,2)	-2,03 (2,14)	-1,93 (2,14)	< 0,001
LANGUAGE					
Boston Naming (immediate naming)	80	26,2 (3,0)	-0,74 (1,34)	-0,79 (1,27)	< 0,001
Famous Faces (naming %)	80	89,8 (11,5)	-0,06 (1,18)	-0,64 (1,19)	< 0,001
Proverbs (number correct)	73	7,0 (2,3)	-0,51 (1,05)	-0,12 (1,05)	NS
MEMORY					
Digit Span - forward	82	10,5 (2,1)	-0,40 (1,17)	-0,18 (1,13)	NS
backward	82	7,6 (1,9)	-0,56 (1,08)	-0,41 (1,01)	< 0,001
List Learning					
Number recalled	82	60,8 (16,6)	-1,12 (1,46)	-0,51 (0,88)	< 0,001
Retention 10 min.	82	8,2 (1,7)	-0,49 (1,50)	-0,95 (1,45)	< 0,001
Rey's Figure (recall after 3 min.)	67	17,9 (6,6)	-0,82 (0,96)	-0,66 (0,94)	< 0,001
EXECUTIVE FUNCTIONS					
Controlled Oral Word Association (animals + words with s)	82	34,8 (10,1)	-0,90 (1,16)	-0,96 (1,15)	< 0,001
Raven Advanced (number correct)	71	7,6 (2,2)	-0,43 (1,07)	-0,30 (1,03)	< 0,05
Design Fluency (number of different designs)	71	24,7 (8,1)	-1,38 (1,29)	-1,26 (1,25)	< 0,001
Calculation	81	15,4 (3,6)	-0,31 (0,92)	-0,20 (0,96)	NS
Tower of London (number of moves)	67	65,4 (11,6)	0,13 (0,92)	0,10 (0,95)	NS
ATTENTION/MENTAL SPEED					
Stroop Test (number of correct)	78	47,7 (1,7)	-0,98 (0,96)	-0,89 (1,17)	< 0,001
Auditory Motor Attention (20-errors)	78	18,3 (1,5)	-1,13 (1,34)	-1,18 (1,37)	< 0,001
Symbol Digit Test (no. correct in 90 sec.)	69	39,0 (10,3)	-1,53 (0,96)	-1,33 (0,98)	< 0,001
Proverbs (sec.)	73	238,0 (108,7)	-1,0 (1,04)	-0,80 (1,03)	< 0,001
Raven Advanced (sec.)	71	433,9 (185,1)	-1,51 (0,87)	-1,33 (0,97)	< 0,001
Tower of London (sec.)	67	263,3 (104,1)	-1,11 (1,16)	-1,15 (1,19)	< 0,001
AVARAGE RESIDUAL OF 9 TESTS **	82		-0,67 (0,55)	-0,70 (0,58)	< 0,001

Mean scores and SD in brackets. * One-sample t-test (one-tailed). ** The average normalised and residual index scores (nine tests), used to assign Dementia Index (DI) scores in MS3.

may not necessarily be close to zero (depending on both possible errors in the estimated regression coefficients and sample size). For a similar analysis, Rubin developed a complex formula that took both factors into account when testing mean residuals in drug exposed samples and using regression equations obtained in control groups [151].

Rubin's formula could be used in this study if it could be assumed that the variance of the residuals were similar in the MS3- and control groups. In general this could not be assumed because the variance of the residuals in the MS3 group will depend on both "normal" unexplained variance and the variance associated with the variance of the disease. Consequently, it was decided to base statistical tests on the observed variance in the MS3 group only and to use one-sample t-tests to test the statistical significance of deviations from zero in mean residuals.

Of the 23 test indices examined, 6 did not differ significantly from 0 in the one-sample t test (one-tailed) - WAIS Vocabulary, WAIS Information, Proverbs (number correct), Digit Span (forward), Calculation, and Tower of London (no. of moves). Measures of verbal intelligence did not differ between the two groups. In all other cognitive domains impairment was present in two or more mean test scores. Without exception all tests of attention/mental speed revealed significant impairment in MS patients. The skewness of residuals were close to 0 (range 0,03 - 0,38).

The number of tests completed shows that not all tests were completed by all patients, and the reasons for this are described in table 4.3.3.

Table 4.3.3 Completion codes (CC)*

Test	N	CC1	CC2	CC3	CC4	CC5
Street	79			3		
Rey's figure	67	11			4	4
Boston Naming	80			1	1	1
Famous faces	80			1	1	1
Proverbs	71		4	3	4	2
Raven	71			3	8	3
Design fluency	71	11				1
Calculation	81				1	1
Tower of London	67	11			4	4
Stroop	78			3	1	1
AMA	78	4				
SDMT	69	11		1	1	1

*** Completion codes (described in section 4.2): Test not completed due to: CC1 - Motor or sensory disability, CC2 - poor reading abilities, CC3 - visuospatial disability, CC4 - poor concentration, fatigue or lack of time. CC5 - the test was not completed, but could presumably be completed under optimal circumstances.**

Not surprisingly motor and/or sensory dysfunction are the main obstacles of neuropsychological testing in MS. Completion codes of visuoperceptual impairment do not indicate major problems of this kind, though the visual system often is affected by MS. Raven Progressive Matrices often had to be interrupted due to poor concentration. The number of tests completed and the completion codes 1-4 sum up to 82, which is the number of patients in the MS3 group. CC5 is an additional score which is only assigned when the examiner judged that the patient could have passed the test under other circumstances (e.g. less fatigued).

Frequency of dementia

Based on the criteria described in the methods, a dementia index (DI) was computed (table 4.3.4). Using DI score 5 as the cut-off score for dementia, 54,5% of the patients in the study

Table 4.3.4 Dementia Index

	DI score	% of the total study population	MS1[1)]	MS2[1)]	MS3[1)]	Control group I [2)]	Control group II [2)]
NO DEMENTIA 45,5%	0	15,2%			18,3%	65,3%	62,5%
	1	7,1%			8,5%	6,7%	12,5%
	2	8,1%		9,1%	8,5%	10,7%	21,9%
	3	10,1%			12,2%	8,0%	3,1%
	4	5,1%	16,7%	9,1%	3,7%	5,3%	
DEMENTIA 54,5%	5	12,1%		18,2%	12,2%	1,3%	
	6	8,1%			9,8%	1,3%	
	7	5,1%		9,1%	4,9%		
	8	8,1%	50,0%	9,1%	4,9%		
	9	5,1%		18,2%	3,7%	1,3%	
	10	5,1%		9,1%	4,9%		
	11	2,0%		18,2%			
	12	9,1%	33,3%		8,5%		
	MEAN DI [3)]		8,7 (±2,7)	7,4 (±2,9)	4,5 (±3,7)		

1) The relative distribution of DI scores within the patient groups.
2) Percentage of the control subjects classified according to the same criteria as the patients.
3) MS1 and MS2 are both significantly more demented compared to MS3.

population were classified as demented. The relative distributions of DI scores are shown for the entire MS group, MS1, MS2, and MS3. Not unexpectedly the frequency of dementia is higher in MS1 and MS2 and on average these groups are significantly more demented compared to MS3. The distributions of DI scores computed for the two control groups show

that 4% in Control Group I and none in Control Group II were classified as demented using the criteria of DI.

Correlations between Dementia Index and other variables

The DI scores of the 99 MS patients were correlated with a number of measures. There was a significant correlation between DI and MMSE (r = 0,44; P < 0,001). However MMSE classified only 14% of the MS patients as demented, using the recommended cut-off score of 24 (39% were classified using 28 as cut-off).

Table 4.3.5 Background of the dementia versus no-dementia groups.

	NO-DEMENTIA mean (S.D.)	**DEMENTIA mean (S.D.)**	P =*
Age	42,2 (4,0)	42,3 (4,6)	NS
Female/male ratio	1,8	1,6	
Vocational training	13,7 (2,1)	11,8 (2,1)	< 0,001
Onset of disease	11,6 (4,0)	13,4 (4,4)	< 0,05
Time since diagnosis	7,9 (4,1)	9,3 (4,5)	NS
EDSS	4,9 (2,0)	6,1 (2,2)	< 0,01
NRS	65,9 (16,1)	50,1 (23,6)	< 0,001
AI	3,9 (2,7)	5,5 (3,1)	< 0,05

*** Mann Whitney**

None of the disease variables age (r = -0,04), time since diagnosis (r = 0,16) and disease duration (r =0,15) were significantly correlated with DI, but there were a significant correlation between vocational training and DI. There was no difference in age, disease onset, and time since diagnosis between the dementia group and the no-dementia group (table 4.3.5). Demented patients had significantly lower vocational training and time since onset of disease was significantly higher in this group. The correlations between DI and the neurological rating scales were all modest but reached significance: EDSS (r = 0,35), NRS (r = 0,45), and AI (r = 0,32). However, on a group basis MS patients with dementia were significantly more impaired on the EDSS, NRS, and AI. 42% MS patients with mild, 42% with moderate, and 64% with severe neurologic impairment according to EDSS were classified as demented.

The ratio between females and males was almost evenly distributed in both dementia groups, with 2/3 females and 1/3 males (table 4.3.6). There were no significant gender differences in age, onset of disease, EDSS and AI (Mann Whitney).

Table 4.3.6 Dementia versus gender

	No-dementia	Dementia
Male	18 (18,2%)	19 (19,2%)
Female	27 (27,3%)	35 (35,4%)

Chi-Square test = N.S., percentage of the study population in brackets

The average grade of dementia was significantly higher in patients with a primary progressive (PP) course of the disease and patients with a secondary progressive (SP) tended to be more demented (p = 0,06), compared to the relapsing remitting (RR) group (table 4.3.7). This is mirrored in a higher proportion of dementia cases in these groups Ten of the RR patients had a benign course of the disease, and none of them were classified in the dementia group. In the SP group there was an almost even distribution between demented and non-demented, whereas two thirds of the patients with PP course were in the dementia group. There were significant differences regarding neurological impairment (EDSS) in all group comparisons. There were no between groups difference regarding age, but patients with SP tended to have longer disease duration than MS patients with RR.

Table 4. 3.7 Course of disease versus dementia and other variables.

Course of disease	DI [1] mean (SD)	Dementia % [2]	Age mean (SD)	EDSS [3] mean (SD)	Disease duration [4] mean (SD)
RR (n = 27)	3,6 (2,9)	40%	41,1 (4,3)	3,4 (1,8)	11,7 (3,5)
SP (n = 53)	5,3 (4,1)	57%	42,8 (4,2)	6,1 (1,6)	13,5 (4,2)
PP (n = 19)	6,6 (3,3)	68%	42,6 (14,4)	7,3 (1,6)	11,1 (5,1)

1) p < 0.05 for RR versus PP and p = 0,06 for RR versus SP. 2) Percentage of the disease groups classified as demented. 3) All groups differed significantly from each other. 4) p = 0.054 for RR versus SP.

41 patients, corresponding to 41,4% of the study population received some kind of medicine at the time of examination (antidepressants, hypnotics, psychoactive drugs, antispastic drugs and/or analgesic). The mean DI score for medicated patients (6,1 (±4,1)) were significantly higher than for the patients who were not medicated (4,4 (±3,3)) (Mann Whitney, p < 0,001).

Mood disorder in MS3

HDS scores classified 73,2% of the patients in MS3 as “not depressed”, 25,6% as “mildly depressed”, and 1,2% as “severely depressed”. Patients who were rated as depressed on HDS were more impaired on EDSS ($p< 0.01$) than non-depressed, but the groups did not differ in age and disease duration. HDS and Beck-abbr. were significantly correlated ($r=0,66$; $p < 0.001$). The patients with dementia were more depressed (HDS) and reported more anxiety (STAI-state) than the patients without dementia (table 4.3.8). Beck-abbr. revealed no difference in the patients’ self-rating of depression. The present level of anxiety reported by the patients was significantly correlated to degree of neurologic impairment ($r = 0.25$; $p < 0,05$), and both measures of depression (HDS ($r = 0,60$; $p < 0,001$) and Beck-abbr. ($r = 0,54$; $p< 0,001$)), but not to age and disease duration. The two anxiety scales were significantly correlated ($r = 0,66$; $p < 0,001$). There were no difference in reports of general level of trait anxiety (STAI-trait) between demented and non demented patients.

Table 4.3.8 Psychiatric scales in MS3 dementia versus no-dementia groups.

	NO-DEMENTIA mean (S.D.)	DEMENTIA mean (S.D.)	P *
Beck-abbr.	4,3 (4,0)	5,2 (5,6)	ns
HDS	4,6 (3,4)	6,3 (4,2)	p<0.05
STAI-state	27,7 (5,2)	33,2 (9,1)	p<0.01
STAI-trait	35,1 (8,1)	36,6 (9,8)	ns

*** Mann Whitney**

Table 4.3.9 shows the association between course of disease and the psychiatric scales for the MS3 group.

Table 4.3.9 Course of disease versus psychiatric scales in the MS3 group alone.

Course of disease mean (SD)	HDS [1)]	Beck-abbr. [1)]	STAI- state [2)]	STAI - trait [2)]	DI [1)]
RR (n = 26)	3,6 (2,6)	2,8 (2,6)	29,5 (6,0)	34,0 (7,5)	3,5 (2,7)
SP (n = 46)	6,2 (4,1)	5,3 (5,3)	30,7 (7,8)	36,8 (9,7)	5,2 (3,9)
PP (n = 10)	6,8 (3,9)	7,2 (5,1)	31,0 (11,4)	35,8 (8,7)	5,7 (3,2)

1) Both SP and PP significantly worse than RR, no difference between SP and PP (Mann Whitney)
2) No significant difference between groups (Mann Whitney)

RR patients are significantly less affected on both measures of depression, whereas there are no differences between the groups according to actual level of anxiety (STAI-state) and

general level of anxiety (STAI-trait) reported. In contrast to the DI scores for the entire study population (table 4.3.7), level of dementia did not differ between the SP and PP group. As expected, SP and PP patients had significantly more neurologic impairment (EDSS) that RR patients. There were no differences between groups in age and disease duration.

4.4. Discussion

In accordance with a number of previous studies, this study shows that cognitive impairment is present in a very large proportion of MS patients. Furthermore cognitive impairment encompasses a broad range of cognitive functions. The pattern of cognitive dysfunction is based on neuropsychological assessment of the 83 % of the total study population who were able to co-operate sufficiently. The MS1 and MS2 subgroups are interesting, because these patients are often excluded in neuropsychological studies due to their lack of ability to co-operate. Analysis of the patients in these two subgroups compared with MS3 revealed no differences in demographic variables and disease duration, but neurological impairment scores were significantly elevated. The dementia index scores classified patients from the MS1 and MS2 groups from mild/moderate to severe dementia, indicating that most of these patients were more or less cognitively affected. These results indicate a possible bias in prevalence studies which only include MS patients capable of co-operating in comprehensive neuropsychological test batteries (e.g. [142]).

Pattern of dysfunction

The cognitive domains most often affected by MS are memory, attention, and executive functions, as described in the review of the literature. Performance in tests of verbal intelligence was not impaired in the MS-group, and previous studies also indicate that these tests are less vulnerable to the effects of MS pathology than performance subtests [140]. The two visuospatial tests were both significantly impaired in MS patients. The Street test indicated a deficient visual closure function in MS, but as the Completion Codes indicates, vision per se was not impaired in this group. Spatial constructional abilities are difficult to measure. Only 67 patients were able to draw a copy of the Rey's Complex Figure mainly due to impaired motor function. Although visuoperceptual and spatial performance were impaired, this visuoperceptual dysfunction caused no major problem for the patients' ability to co-operate in the neuropsychological assessment.

Most studies have reported preserved naming abilities in MS patients (e.g. [15,74,116,142]), but in this study Boston Naming Test scores were significantly below those of normal controls. Likewise the naming of famous persons was impaired. Other studies have reported similar

results on the Famous Faces Test [15,17,142]. This task seems to differ from the Boston Naming Test, in placing higher demands on remote memory function.

A multiple choice version of the Proverbs Test has not been used previously. This particular version of the Proverbs Test was chosen to ensure a "pure" measure of the ability to identify verbal abstractions, uninfluenced by the persons' ability to formulate and express thoughts. The test could not be used in all cases due to dyslexia, visual impairment, or poor concentration. In this study the MS patients performed close to the normal controls. The result is contrary to the clinical impression that even mildly affected MS patients often claim to have problems with verbal thinking and abstraction. However, this contradiction may be due to the fact that the proverbs test not necessarily tap the kind of "verbal abstraction" referred to by these patients. One obvious difference between the cognitive demands in this test and real life situations is that the test specifies some possibilities to choose among, whereas in a real situation the person has to focus on relevant aspects of the information and generate the abstract content.

The results of the digit span tests illustrated quite well the contradictory results in previous studies of immediate memory span and working memory. This study indicated a failure in working memory, but not in the ability to simply keep a few digits in mind. In accordance with previous studies (e.g. [54,82,142]) MS patients were impaired on all measures of secondary memory, both verbal and non-verbal. List Learning revealed problems with both learning and subsequent retrieval of verbal material. Memory is a complex cognitive function, very vulnerable to almost anything affecting the brain (e.g. head trauma, anoxia, stroke, depression). There may be a link to the executive problems of generating and maintaining strategies frequently observed in MS patients. However, the nature of memory disorder in MS is still not understood, and the questions regarding retrieval or acquisition impairment still remain controversial (e.g. [21]).

The performance in tests sensitive to executive functions gave ambiguous results. As expected, Controlled Oral Word Association was impaired and so was the performance in a non-verbal fluency test - Design fluency. In Design fluency the person was asked to draw as many different designs as possible in three minutes, connecting five dots in different ways.

Eleven patients could not perform this test due to motor dysfunction, but the remaining patients produced significantly fewer designs than controls. This test among other things places high demands on the ability to generate and maintain a strategy. The Raven Progressive Matrices Test (RPM) was impaired in the MS group, but in 8 cases this rather demanding test had to be discarded due to poor concentration. Calculation revealed no differences between groups. It is questionable how well calculation is categorised under the heading “executive functions”. Calculation surely may put demands on “coping with novelty”, strategy, logic and set shifting, but it may also be viewed as more automatic processes, based on a number of over learned algorithms, demanding working memory capacity.

The Tower of London test (ToL) (a.m. Shallice) is the only test used in this study which is based on theories about executive functions and specifically developed to measure this kind of cognition. However, the patients’ ToL results did not differ significantly from those of the controls, and the average performance of the patients was even slightly above expected levels. This is in accordance with previous studies, showing ambiguous results using the same ToL version [165,166]. It is also my experience from a number of patients with severe head trauma that patients often perform at the level of normal controls in this test. In earlier studies computerised versions of the ToL test revealed significant differences in accuracy of solutions (number of moves to solution and minimum moves) between patients with various aetiologies [125,153]. Patients with frontal lobe excisions took for example significantly more moves to solve the problems [125].The difference between computerised and non-computerised versions may simply be differences in the cognitive requirements between the two versions. The “wood version” used here may be more structured and “concrete”, compared to the computerised version which probably puts higher demands on “internal mental structure”, attention, and working memory.

Performance on tests measuring attention and mental speed was unequivocally impaired. In a modified, and rather easy, version of the Stroop Test MS patients performed significantly below controls, which is in accordance with previous findings (e.g. [45,74,142,185]). Likewise performance in the Auditory Motor Attention test, demanding selective responses, was

impaired. Together these results indicate problems of focused attention or selective response selection in MS patients.

No measures of divided attention were included in the test battery, but as described in the section on attention, speed of information processing (capacity limitations) is sometimes considered an aspect of divided attention. As expected MS patients performed worse than controls on the Symbol Digit Modalities Test (SDMT). Although SDMT is sensitive to brain dysfunction in general, a large proportion of the patients could not perform the test due to motor impairment, and for the patients who performed the test it may be speculated that motor dysfunction contributed to the slowness.

In Raven Progressive Matrices (RPM), ToL, and the proverbs test, the time to solve each subtask was recorded in an attempt to quantify slowed information processing. In two of the tests the time scores revealed a more or less “pure” measure of mental processing time, whereas ToL also involves a motor component. Interestingly, all these measures of the “speed of mental processing” revealed significant reductions in the MS group. In RPM the patients used more time to solve the tasks, but on a group basis they also failed the test, which could mean that the increased processing times simply were due to lack of skill to solve the task. However, the correlation between performance and time was as low as 0,06, and the average residual score of time for patients performing better than the mean of the controls (n = 29) was -1,3 (±1,1), indicating a weak relationship between “skill” and processing time in RPM. In the two other tests the patient groups performed the tests at levels comparable to the controls in terms of error scores, but spent significantly more time thinking and/or moving. In general these results indicate a decrease in speed of cognitive performance, which is a complaint frequently heard from MS patients.

In conclusion, the pattern of cognitive dysfunction in this sample of MS patients is generally in accordance with the results reported in previous studies. The results indicate the MS may affect both individual cognitive abilities and/or the speed of cognitive processing.

Frequency of dementia

An important aim of this study was to examine the frequency of general cognitive impairment in the study population. Using the criteria of dementia described under methods 54,5% were classified in the dementia group. The prevalence of dementia was based on different kinds of information about cognitive function, but the criteria for dementia seem rather conservative, classifying only between 0 and 4 percent of the controls as demented. The prevalence of cognitive dysfunction in this study approximates the level in some of the earlier studies [54,108,142], but the studies are not directly comparable due to differences in recruitment, disease variables, neuropsychological test batteries, data analysis, criteria for failed tests, etc.

The study population was planned for simultaneous use in this study and another study correlating clinical parameters and MRI [163]. To satisfy the methodological requirements in the second study, the study population was limited to patients between 35 and 50 years old, with a disease duration between 5 and 20 years, drawn from a community based register by an uneven random selection in nine strata. The study population was therefore not a cross-section of the true MS population between age 35and 50 years old. For this study one might ideally have preferred a more representative sample of the MS population, but this was not possible. However, the study candidate population is a well defined population-based group, which is seldom in this field of research.

The non-responding group tended to include patients with slightly more disability, but otherwise the study population was not biased severely. This study included all patients who accepted to participate, irrespective of the severity of MS. The study therefore includes two types of patients who are underrepresented in most other studies. Firstly, patients with very severe disability are often excluded in MS studies. Secondly, patients with a benign course frequently are not treated by MS clinics or neurologists, which are the bases of recruitment in most other studies. In this study 6 of the MS patients were so disabled that they could not be tested at all, and 10 patients had a benign course of the disease (16% of the study population).

The inclusion of all patients irrespective of their disablement has the disadvantage that measures of cognitive ability are not directly comparable. In this study the problem was solved by transforming test scores to a common dementia index scale (DI), according to theoretically based and well defined criteria. However, use of this method requires a

reasonable equivalency of DI scores in the three MS subgroups. Patients in MS1 could by definition not be tested, but ideally some of the patients in the MS3 group should also have been tested with the mental status examination tests (MS2). This was unfortunately not done in the study. Eleven neurologic patients were subsequently examined with both MS2 and MS3 tests in an attempt to evaluate the internal consistency of DI scores. This analysis revealed a significant correlation between DI scores based on different test batteries in these patients. The correlation between DI scores and Mini Mental Status Examination (MMSE) was modest, but reached significance. MMSE is notoriously not a sensitive measure of dementia (see section 3.1), and no high correlation was therefore to be expected. Together these data indicate that some level of internal consistency is present in the Dementia Index.

Previous studies of the prevalence of cognitive impairment in MS differed with respect to a number of variables in addition to these mentioned above (Table 4.4.1).

Table 4.4.1 Studies of the frequency of cognitive impairment in MS.

Study	Number of patients	Age mean (S.D.)	Disease duration mean (S.D.)	Neurological disability (mean)	Course of disease	Sex ratio F/M	Prevalence of cognitive impairment
Heaton et al. [68]	100	37,4 (8,3)	9,4 (5,9)	DSS 3,1	57% RR 43% CP	3,0	57%
Comi et al. [33]	64	-	-	-	-	-	47%
Pia Amato et al. [3]	50	29,9 (8,5)[1)]	1,5[1)]	EDSS 2,0[1)] EDSS 2,6[2)]	88% RR 12% CP	1,8	78%[1)] 100%[2)]
Beatty et al.[20]	103	42,2 (9,3)	16,1 (9,6)	AI 3,5	-	1,7	62%
Franklin et al. [54]	60	37	14,6	EDSS 5,3	100% CP	1,3	60%
McIntosh et al. [108]	147	48	13	EDSS 6,0	-	1,8	46%
Rao et al. [142]	100	45,7 (11,3)	14,2 (10)	EDSS 4,1	39% RR 19% CP 42% CS	3,0	40%
This study	**99**	**42,2 (4,4)**	**13,6 (4,3)**	**EDSS 5,6**	**27% RR 54% SP 19% PP**	**1,7**	**54,5%**

Note: **(E)DSS: (Expanded) Disability Status Score, RR: Relapsing remitting, CP: Chronic progressive, CS: Chronic stable, PP: Primary progressive, SP: Secondary progressive. 1) Initial examination 2) Follow up examination.**

The mean age in this study was close to the mean age in some other studies [20,142], but the range was smaller because age was part of the selection criteria. The disease duration was close to that of some other studies [54,108,142], but again the range was smaller in this study. The

average neurological disability was close to that of two of the other studies [54,108], but generally more severe. The descriptions of disease course look very different, but this parameter is difficult to compare across studies due to important differences in definitions [100]. Finally the female/male ratio was close to the ratio in most other studies, about the expected level of 1,5 - 2,0 [169].

Three previous studies [33,108,142] and the present study found a prevalence of cognitive dysfunction at about 40 to 50 % . The study by Comi et al [33] is not comparable, because disease variables were not reported separately for the subgroup which was tested. The study by Rao et al. [142] is noteworthy for several reasons. It is a very careful study, with a broad range of MS patients who were carefully examined and compared with a matched control group. Like the present study, data analysis was based on individually calculated residuals based on regression analysis. However, the patients were less neurologically disabled and almost three times as many women as men were included. The study by McIntosh et al. [108] resembled the present study regarding recruitment of patients, neurological disability, disease duration, and sex ratio, but the criteria of dementia were far from comparable. McIntosh et al. used published norms of the individual tests, and “dementia” was defined as evidence of impairment in one or more of the test areas. In general, these three studies are based on large and well defined groups of MS patients, and in spite of the methodological differences mentioned above, all studies found prevalence rates around 40 to 50%. This might indicate a general level of the prevalence of cognitive impairment in MS.

There are several possible reasons for the higher prevalence rates reported in some of the other studies mentioned in table 4.1.1 [3,20,54,68]. The composition of the study populations concerning disease course differs markedly from that in the study by Rao et al. [142] and the present study. Patients in the studies with higher rates of cognitive dysfunction were not more neurologically disabled, and in two studies [3,68] they were even less disabled than the patients in the three studies compared above. A higher proportion of relapsing remitting patients and less neurological impairment cannot explain the high prevalence of cognitive dysfunction. On the contrary, the prevalence should be lower in such populations. However, referral bias may be an important factor in these studies [122]. The patients were recruited from local MS centres

or participated in clinical trials, which might bias the selection towards patients with more disabling MS related sequelae.

In conclusion, the present study clearly demonstrates that cognitive impairment affects a considerable proportion of the patients in a random stratified MS population. It is difficult to compare the prevalence rates between studies, but in the few representative studies matching this study the prevalence tends to be between 40 and 60 %.

Dementia Index scores and other disease variables

The mean age, onset of disease, and time since diagnosis did not correlate significantly with DI scores, and likewise group comparisons between patients with and without dementia revealed no differences concerning these variables. Some studies have reached similar results whereas other studies have not, and no unequivocal relationships seem to exist between theses variables [20,68,142]. Although this study is not longitudinal, the results seriously challenge the dominating view of twenty years ago, namely that dementia primarily affects patients with a long disease duration.

The correlations between measures of neurological disability and dementia index scores in this study were modest (although significant), but there were highly significant differences between the dementia and no-dementia groups concerning the measures of neurological disability. The results are in accordance with Rao et al. [142], but not with Heaton et al. [68] and Beatty et al. [20] who found poor associations between neurological disability and cognitive function. This discrepancy might partly be explained by a more restrictive inclusion of neurologically impaired patients in these studies. Although the studies are not directly comparable, the patients in the study by Rao et al [142] and this study tend to be neurologically more impaired. Table 4.3.1 illustrates a tendency for the majority of the neurologically relatively more disabled patients in MS1 and MS2 to be classified in the dementia group. Consequently the inclusion of patients with high EDSS scores might cause a better correlation between cognitive and neurological impairment.

The proportion of females and males in the dementia and no-dementia group was almost even, and comparisons between the gender groups revealed no significant differences regarding age, disease duration, EDSS, and Ambulation Index.

The frequency of dementia in patients with primary (68%) and secondary progressive (57%) MS was higher than in patients with relapsing remitting MS, where only one third were classified in the dementia group. The same tendency for RR patients to be less impaired has been reported by other studies (e.g. [33,68,142]). The same pattern were present for EDSS, where RR patients were significantly less affected than the other two groups. As expected the RR patients tended to have shorter disease duration than the SP group, but there was no difference in disease duration between RR and PP patients.

41 % of the patients received some kind of medication at the time of the examination, and this is about the same percentage as in the study by Rao et al. [142] (43%). The mean DI score was significantly higher in the medicated patients, and potentially medication might have influenced the frequency of dementia. Rao et al. [142] only found a tendency for medicated patients to fail more tests. The association between DI and medication might partly be explained by the association between dementia and neurologic impairment, because antispastic medicine was the most common medicine used. If antispastic drugs are excluded from the analysis only 20,2% of the patients took prescribed medicine. The results about medication effect in neuropsychological MS studies are diverging (see section 3.1). The control of medication effect in studies like this is very difficult. Different kinds of medicine has different and highly individual effects on cognition.

In conclusion, the results do not indicate strong associations between cognitive impairment and age, gender or disease duration, but patients with dementia were significantly more neurologically disabled. Patients with a RR course of the disease tended to be less cognitively deteriorated. Medication might potentially effect cognitive performance in this study.

Mood disorder

The Hamilton Depression Scale (HDS) classified 26,8 % of the MS3 group as depressed. This prevalence of depression is in accordance with other studies of depression in MS [117]. Patients with depression were significantly more neurologically impaired than non-depressed, whereas age and disease duration revealed no significant group differences. The MS3 patients with dementia were significantly more depressed on HDS than patients without dementia, whereas the abbreviated version of Beck Depression Inventory (BDI-abbr.) revealed no difference between these groups. This difference may be explained by a lower sensitivity of BDI-abbr. due to the missing questions. Another explanation may be unrealistically low self ratings among demented MS patients.

The results illustrate that moderate depression is frequent, affecting more than one fourth of the study group. Depression is related to cognitive and physical deterioration, but not to disease duration and age. Although the relationship is of a rather complex nature (see section 2), there seems to be a correlation between degree of brain pathology and cognitive/neurologic impairment. Depression in MS is therefore probably not solely of a psychological nature, but might also be influenced by some organic factors. Depression alone might contribute to part of the cognitive impairment, but only about one fourth of the MS3 patients were depressed, indicating that this factor probably has a limited influence on cognition.

The State Trait Anxiety Inventory (STAI) revealed no differences in the basic anxiety level of patients in the dementia and no-dementia groups (STAI-trait). However, patients in the dementia group reported a significantly higher level of present anxiety (STAI-state) than patients without dementia. This means that despite an almost similar “disposition to anxiety” patients with dementia felt somewhat more anxious in the situation. There was a significant relation between level of anxiety reported and level of neurologic impairment. The anxiety reported might therefore partly be caused by the anxiety provoking feeling of “deteriorating cognitive and physical control” in some of the patients, which is familiar to most clinicians.

Analysis of disease course revealed a general distinction between the relapsing remitting (RR) course and the two progressive courses - secondary progressive (SP) and primary progressive (PP). Patients with a progressive course of the disease were significantly more affected on

both measures of depression compared to RR patients. Likewise the progressive patients were neurologically more impaired and had higher DI scores than RR patients. Measures of anxiety revealed no differences between groups. These results confirm the general tendency reported in the literature, namely that patients with a primary progressive course of the disease are more cognitively affected than RR patients, and the same seems to be true for depression. However, as described in section 2.3 it is often difficult to compare results between studies, due to differences in the definition of the disease courses.

In conclusion depression is present at about the same level as seen in other studies. Patients in the dementia group reported higher levels of anxiety. Patients with RR were significantly less depressed than patients with a progressive course, whereas measures of anxiety revealed no differences for course of disease. The effect of depression and anxiety on cognitive performance in the MS patients remains questionable. Brain involvement seems to play a role for both level of depression and anxiety, but this relation is probably complex in nature, including interaction between biological, psychological and social factors as described in section 2.5.

5.0. CONCLUDING REMARKS

This thesis has focused on a very important issue in multiple sclerosis (MS) research - the prevalence and nature of cognitive impairment in a randomly selected, stratified, population-based study population. The attempt to create a coherent picture of the cognitive function in MS has been rather confusing due to the very unstable and variable nature of MS. MS research may be illustrated by the analogy of a large number of researchers from all over the world trying to create a movie by taking one picture each. There are a lot of pictures of for example pathology, epidemiology, and memory impairment, but they were created under different conditions, with different motives and by different techniques. It is possible to put a short string of memory pictures together, but what can be seen by running this memory movie on a screen is rather “flickering”.

In section 2 and 3 the literature on cognitive impairment in MS was reviewed. In spite of all the methodological problems, the review left no doubt that a large proportion of the MS patients was cognitively impaired, and that memory, attention, and executive functions were among the frequently deteriorated functions. However, at the same time the review demonstrated a lack of knowledge about the detailed nature of the impairment. The tests used were standard neuropsychological tests, which were often unsuitable to answer more specific questions about the cognitive domains. In order to get a more precise understanding of cognitive impairment more knowledge about the task requirements of cognitive tests is necessary. The methods used in cognitive neuropsychology may be inspiring for this work.

The review also illustrates some central methodological issues in the study of MS. In spite of the developments in the paraclinical diagnostic techniques, MS may still be difficult to diagnose. The duration and course of disease may be difficult to define in some patients. The studies concerned patients ranging from mildly disabled to severely disabled who were completely dependent on the help from others. Studies of MS have to encompass this variability and therefore ***patient selection*** is very important. In most MS studies patients were recruited from MS centres and MS societies, and in general such study populations are biased towards more disabled patients. It should be obvious that highly selective populations are not

suitable for general conclusions about MS (e.g. memory, attention, fatigue), whereas they may be ideal for intervention studies.

Another methodological issue concerns the neuropsychological examination. There seems to be little agreement on the most appropriate selection of ***neuropsychological tests***. The use of different tests makes comparisons across studies difficult or impossible. Furthermore the selection of tests has to take the testability of the patients into account. Due to the range in severity of disability there is a paradox in test selection. No single neuropsychological test is able to make fine discriminations throughout the true range of cognitive dysfunction in MS. This problem has most often been solved by excluding patients unable to co-operate reliably. In this study another approach was chosen, namely to include all patients and afterwards scale the various kinds of information on a common dementia index.

The selection of the ***appropriate control group*** is a classic methodological problem, for which the reviewed studies presented different solutions. Most studies used healthy controls, but the choice of control group should depend on the individual research question. In some study designs it may be interesting to compare the performance of MS patients to patients with other neurological diseases. In studies using healthy controls there were differences in the matching criteria, but in most studies MS patients and controls were matched on the basis of age and sex. Not all studies used education as matching criterion, allthough education is known to be important for neuropsychological test performance (e.g. [7,119]).

Closely related to the differences in selection of neuropsychological tests and control groups are differences in ***data analysis and definitions of cognitive impairment***. Most studies used a percentile score in the normal control group as a cut-off score, but there were major differences in the criteria for general cognitive impairment (e.g. two or more failed tests). Only a few studies used multiple regression analysis to correct the individual test scores for the influence of demographic variables. Studies without this kind of correction may tend to overestimate intellectual impairment in eldery low-education patients and underestimate intellectual impairment in young high-education patients[119].

These are important factors that might affect the results of cognitive MS research. However, the ideal study design does not exist and in research one always has to choose among several possibilities. In 1990 Peyser et al. [130] published guidelines for neuropsychological research in MS and suggested sampling methods, control groups and recommended a core battery of neuropsychological tests. The overall conclusion regarding the literature and the methodological issues reviewed here is that these recommendations are still as pertinent today.

The study described in this thesis involved the participation of almost 100 MS patients. Most of the patients agreed to spend a whole day at the neurological department to complete the neuropsychological examination. A large proportion of these patients felt relieved by the opportunity to talk about their cognitive impairments. They told about memory impairment, attentional problems, lack of overview, and emotional flatness, which are well known to most clinical neuropsychologists. Even patients with a benign course and unimpaired test performance, claimed to have minor cognitive problems of this kind in their everyday life. The general lesson taught by these MS patients is that patients and their relatives need more information and support about cognitive dysfunction.

A study like this provokes some speculations. What is the ecological value of the neuropsychological tests? What does a raw score of 7 in word retrieval, or a dementia index score of 9, mean to the patient? Do these values reflect anything essential for the patient at all? Most neuropsychological tests are selected by tradition and because appropriate norms exist. The cognitive domains examined are also chosen by tradition and have not changed essentially for a very long time. The MS patients frequently complained about problems in social interaction, changes in humour, and things like that, which they found to be among the most disabling symptoms. It is therefore likely that an extension of the neuropsychological examination to include some of these “socio-cognitive” abilities would result in more ecological information about the neuropsychological consequences of MS.

In conclusion, the present study confirms the results found in previous studies that about 40 to 60% of the MS population revealed signs of general cognitive dysfunction. For methodological reasons it is difficult to calculate the prevalence of cognitive dysfunction

precisely, but the percentage may well be even higher than 50%. Due to the distributed nature of the disease, MS may potentially affect all kinds of cognitive dysfunction, but memory, attention and executive functions seem to be more prone than other cognitive domains examined. Patients with relapsing remitting MS are not cognitively impaired to the same extent as patients with a progressive course of the disease. No unequivocal relationship exists between dementia and other disease variables in MS. Research in MS is hampered by serious methodological problems and more co-ordinated efforts between researchers seems to be necessary to achieve more insight into the nature of cognitive dysfunction in MS patients. Future research should attempt to widen the concept of “cognitive function” and further explore the relationship between test scores and its relevance in terms of the patients’ everyday life.

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APPENDIX I

A) Disability Status Scale (DSS) & Expanded Disability Status Scale (EDSS)

In 1955 Kurtzke [92] described a 10 point scale for evaluating neurological disability in MS. The impairment is evaluated in eight functional systems (FS), which is graded on a scale from 0 to 5 or 6. The functional systems are: Pyramidal, Cerebellar, Brain Stem, Sensory, Bowel & Bladder, Visual, Cerebral and Other Systems. The Disability Status Scale (DSS) is an overall expression of the ratings in the functional systems, with 10 steps from 0 (normal function) to 10 (death due to MS). In 1983 Kurtzke [93] published an expanded version of the scale, with each of the former steps now divided into two. The two scales are presented below (steps in the original DSS marked with bold).

0	**Normal neurological examination.**
1.0	**No disability, minimal signs in one FS.**
1.5	No disability, minimal signs in more than one FS.
2.0	**Minimal disability in one FS.**
2.5	Minimal disability in two FS.
3.0	**Moderate disability in one FS, fully ambulatory (three/four FS grade 2, others 0 or 1).**
3.5	Fully ambulatory, but moderate disability in one FS (grade 3) and one or two FS (grade 2) - or five FS grade 2.
4.0	**Fully ambulatory without aid; self-sufficient; up and about 12 hours a day despite relatively severe disability consisting of one FS grade 4, or combination of lesser grades exceeding the limits of previous steps. Able to walk without aid or rest some 500 meters.**
4.5	Fully ambulatory without aid; up and about much of the day; able to work a full day; may otherwise have some limitation of full activity. Characterised by relatively severe disability; usually consisting of one FS grade 4 , or combination of lesser grades exceeding the limits of previous steps. Able to walk without aid or rest some 300 meters.
5.0	**Ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities.**
5.5	Ambulatory without aid or rest for 100 meters; disability severe enough to impair full daily activities (FS one grade five or , or combination of lesser grades usually exceeding those for step 4.0).
6.0	**Intermittent or unilateral constant assistance required to walk about 100 with or without resting (usually more than two FS grades of 3+).**
6.5	Constant bilateral assistance required to walk about 20 meters without resting (usually more than two FS grades of 3?).
7.0	**Unable to walk beyond about 5 meters even with aid; essentially restricted to wheelchair;, wheels self in standard wheelchair and transfers alone; up and about in some 12 hours a day (usually more than one FS grade 4+; very rarely pyramidal grade 5 alone).**
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorised wheelchair (usually more than on FS grade 4+).
8.0	**Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms (Usually FS grade 4+ in several systems)**
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions (usually FS grades 4- in several systems).
9.0	**Helpless bed patient, can communicate and eat (Mostly FS grade 4+).**
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow (Usually almost all FS grades of 4+).
10	**Death due to MS.**

B) Ambulation Index (AI)

The Ambulation Index [66] is a simple rating of ambulatory function. The patient is assigned one of the following grades:

0	Asymptomatic, full active.
1	Walks normally but reports fatigue which interferes with athletic or other demanding activities.
2	Abnormal gait or episodic imbalance, gait disorder is noticeable to family and friends. Able to walk 10 meters in 10 seconds or less.
3	Walks independently; able to walk 10 meters in 20 seconds or less.
4	Requires unilateral support (stick, single crutch) to walk; walks 10 meters in 20 seconds or less.
5	Requires bilateral support (sticks, crutches, frame) and walks 10 meters in 20 seconds or less; or requires unilateral support but walks 10 meters in grater than 20 seconds.
6	Recuires bilateral support and walks 10 meters in greater than 20 seconds. May use wheelchair on occasion.
7	Walking limited to several steps with bilateral support; unable to walk 10 meters. may use wheelchair for most activities.
8	Restricted to wheelchair; able to transfer independently.
9	Restricted to wheelchair; unable to transfer independently.

C) Neurologic Rating Scale (NRS)

Neurologic Rating Scale was published in 1984 by Sipe et al [170] as a sensitive method to measure and follow the overall neurological function in MS. A number of neurological systems are tested and assigned a score between 4+ and 4-, indicating increment or decrement of functional activity. Finally these scores are added and form the total NRS score. Low NRS scores indicate severe impairment, whereas a NRS score of 100 indicates no impairment.

System Examined	Maximum Points
Mentation and mood	10
Cranial Nerves	21
Lower cranial nerves	5
Motor	20
Deep Tendon Reflex Spasticity	8
Babinsky	4
Sensory	12
Cerebellar	10
Gait, trunk and balance	10
Maximum total	**100**

D) Incapacity Status Scale (ISS)

ISS [171] is an structured interview evaluating 16 personal competencies - e.g. Grooming, feeding, vision, speech and hearing. Only the score of "mentation" was used in this study.

14. Mentation (Disturbances in memory, reasoning, calculation, judgement or orientation)

0	No observable problem.
1	Disturbance is present but does not interfere with performance of everyday activities.
2	Disturbance interferes with performance of everyday activities; the person may need to use lists or other prompting devices, but manages without the help of other people; the person is likely to be a poor historian.
3	Disturbance is severe enough to require prompting or assistance from others for performance of everyday activities.
4	Disturbance precludes the performance of most everyday activities; may include severe confusion, disorientation, or memory loss.

APPENDIX II

The Allison and Millar [2] criteria in the modified version used by the Danish Multiple Sclerosis Registry[86]:

Probable MS

Clinical signs of involvement of the CNS, which cannot be explained from a single lesion wherever it might be situated. Unequivocal physical signs of at least one of the lesions must be present, but may for other lesions be substituted by abnormal evoked potentials or reliable information of symptoms or physical signs in the past, adequate to localise a lesion typical of MS at a different location. The patient show some physical disablement, a remitting quality of the history, or a stepwise or steady progression over at least 6 months.

Clinically definite MS

Cases with probable MS, but in whom the diagnosis is maintained through the presence of additional neurological findings or symptoms.

Latent MS

Patients who meet the conditions for probable MS, but show slight or no disability. A history of at least two episodes of remitting symptoms separated by a period of at least one month, and unequivocal neurological findings, confirmed by hospital or specialist records, must fulfil the conditions of being explicable only on the basis of multiple lesions. Minimal duration of a symptom to be accepted is 24 hours. If no subjective or objective physical signs were present at the time of the last examination, the evidence of a lesion and the documentation must be so strong that it cannot be ignored. Abnormal evoked responses (prolonged latencies) are accepted as neurological findings, but they do not indicate self-contained lesions, if they are associated with physical signs from the same region of the white matter (e.g. abnormal VEP and a history of optic neuritis).

Possible MS

If the clinical signs of a lesion of the white matter fails to prove involvement at different levels of the neuraxis, or the documentation of such involvement is insufficient, the patients will be classified as possible MS. If the course has been steady progressive from the start and the symptoms and physical signs are confined to the spinal cord, the patients are included only if the progression has lasted for at least 6 months, and oligoclonal band or increased IgG-index have been detected in the CSF.

Discarded cases

Cases, in which the symptoms or findings may as well be caused by other neurological disease, e.g. mild encephalitis, hereditary ataxias, cervical spinal cord compression, or cases in which the physical signs of CNS-involvement are equivocal (cave: neurasthenia, hysteria), and cases in which the suspicion of MS is unwarranted. The discarded cases erroneously notified to the DMSR or with a totally unwarranted MS diagnosis; and 2) "**observational**" cases which cannot pass the diagnostic criteria for the time being, but in which there is a chance that subsequent progression or attacks may confirm the MS-diagnosis.

DANSK RESUMÉ

Indtil for ca. 10-20 år siden mente man at kun alvorligt ramte skelrose patienter med et langvarigt sygdomsforløb blev demente. Forskning har senere vist et helt anderledes billede. Hovedformålet med denne undersøgelse er at undersøge prævalencen af dissemineret sklerose (DS) i en tilfældig udvalgt gruppe patienter, arten af kognitive dysfunktioner, samt sammenhængen mellem kognitiv dysfunktion og DS.

Flere tidligere undersøgelser har fundet mellem 40 og 60 % af DS patienterne dementielt reduceret. Der er ikke fundet nogen sikker sammenhæng mellem demensudvikling og andre sygdomsvariable (f.eks. alder, sygdomsvarighed, forløbstype m.m.). De kognitive funktioner der hyppigst reduceres af DS er indlæring/hukommelse, opmærksomhed og eksekutive funktioner. Forstyrrelser som afasi, agnosi og rum-retningsforstyrrelser er beskrevet, men forekommer sjældent i forbindelse med DS. Der er ikke meget viden om skader i visuoperceptuelle funktioner og dette område er vanskeligt at undersøge da mange DS-patienter har skader i primære visuelle områder.

Aktuelle undersøgelse blev foretaget på Rigshospitalets neurologiske afdeling i perioden 1993 - 1995. I undersøgelsen indgik en stratificeret, tilfældig valgt gruppe sklerosepatienter, udtrukket fra Scleroseregisteret på baggrund af alder (35 - 50 år) og sygdomsvarighed (5 - 20 år). 99 patienter indgik i den neuropsykologiske undersøgelse. 6 patienter var ikke testbare og blev derfor alene klinisk vurderet. 11 patienter kunne gennemføre en kort mental status undersøgelse og 82 patienter gennemførte en mere omfattende neuropsykologisk undersøgelse. Patienternes kognitive funktionsniveau blev skaleret på et demensindex der kategoriserede 54,5% af patienterne som demente. Sammenlignet med raske kontrolpersoner klarede gruppen på 82 patienter sig signifikant dårligere indenfor alle undersøgte domæner (visuospatiale funktioner, sprog, hukommelse, eksekutive funktioner opmærksomhed og mentalt tempo) med undtagelse af sproglig intelligens. Der var ikke forskel mellem demente og ikke-demente patienter med hensyn til alder eller antal år siden diagnose, men der var tendens til at demente patienter havde længere sygdomsvarighed. Demente patienter var, sammenlignet med patienter uden demens, neurologisk signifikant dårligere.

Resultatet af denne undersøgelse er ikke repræsentativt for den “sande DS population.” Undersøgelsens resultater stemmer godt overens med de få sammenlignelige populationsbaserede undersøgelser. Denne undersøgelse adskiller sig fra andre undersøgelser ved at inkludere både meget dårlige (ofte plejehjemsanbragte patienter) og patienter med et benignt forløb. Undersøgelsen bekræfter at en betydelig andel af patienter med DS bliver generelt intellektuelt svækkede som følge af sygdommen, samt at kognitive vanskeligheder kan ramme både tidligt og sent i sygdomsforløbet.