COGNITION AND MULTIPLE SCLEROSIS: A NEUROPSYCHOLOGICAL AND MRI STUDY.

Dissertation submitted in partial fulfilment of the requirements for the degree of Master of Arts in Clinical Psychology.

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Ten people with multiple sclerosis (MS) who felt they had cognitive difficulties because of their MS were investigated. This study had multiple aims. Firstly, to explore the subjective experience of cognitive deficits. Secondly, to assess whether or not there was objective evidence of cognitive difficulties on neuropsychological testing, and whether this was commensurate with a pattern of subcortical dementia. Thirdly, to determine whether their magnetic resonance imaging (MRI) scans replicated the patterns of atrophy frequently reported in MS patients with cognitive difficulties. And finally, to investigate the psychological well-being of the subjects. In depth neuropsychiatric interviews, psychiatric and psychological inventories, a comprehensive neuropsychological battery, and MRI investigations were done.

The mean Full Scale Intelligence Quotient (FSIQ) fell within the superior range, at the 89th percentile. On tests of general intelligence, mental state examinations, there was little or no indication of cognitive deterioration. However, on sophisticated neuropsychological testing, there was convincing evidence of cognitive problems. Magnetic resonance imaging lesions were atypical of the reported research on cognitively compromised MS patients.
The striking feature of this research was the anxiety and stress associated with the neuropsychological tests, and the subjects' uncertainty in regard to their own subjective experiences of cognitive difficulties. Most of the subjects struggled to legitimize their experience of cognitive deficits to themselves and to others, and most subjects were experiencing chronic stressful circumstances, both related and unrelated to their cognitive difficulties. Anxiety and dysthymia, was confirmed on the Millon Clinical Multiaxial Inventory - II (MCMI-II), with subjects' mean scores in the clinically elevated ranges. Acknowledgement and anxiety management should be important components of any cognitive retraining and psychosocial intervention programme. Suggestions for future research are provided.
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1.1. INTRODUCTION

Multiple sclerosis (MS) is a disease of unknown aetiology, affecting the central nervous system (CNS). Historically, the literature has concentrated on the physical sequelae of this chronic, demyelinating disease. It is only recently that research has begun into the cognitive aspects, despite the fact that mental changes were recognized from the earliest accounts (Rao, Reingold, Ron, Lyon-Caen & Comi, 1993).

Attention to cognition in MS has been neglected for several reasons. Firstly, cognition has traditionally been viewed as a function of the cortex (Prosiegel & Michael, 1993) and cortical structures are rarely directly involved in MS (Mendoza, Pugnetti, Saccani & Motta, 1993). It is only recently that white matter disease has been implicated in cognitive function. Secondly, inconsistent findings have complicated a clear understanding of cognitive impairment in MS. Furthermore, the image of many MS patients being 'neurotic' (and thus cognitive symptoms can be viewed as imagined) has also added to the minimalization of cognitive dysfunction in MS. Lastly, as depression is common in
MS, cognitive symptoms can be misdiagnosed as a psuedodementia. It is only with the recent advent of sophisticated neuropsychological and neuroimaging techniques that cognitive dysfunction can be systematically studied.

The debate as to whether affective disorders and cognitive dysfunction are reactions to having MS, or directly caused by the demyelination, or the coincidental occurrences of separate illness (e.g., bipolar affective disorder) (Honer, Hurwitz, Li, Palmer & Paty, 1987), is ongoing. Affective disorders, fatigue and cognitive disturbance in MS are equally important to understand, as they can all influence (even cause) each other.

1.2. PSYCHIATRIC IMPLICATIONS

1.2.1. Anxiety and Neurosis

Multiple sclerosis patients often present with inexact symptoms, with "no" physical cause (Smith, Samkoff & Scheinberg, 1993), and people with MS are frequently misdiagnosed (Feinstein, Du Boulay & Ron, 1992b). In a study of 91 patients with MS, 16% were referred for psychiatric treatment between the onset of initial symptoms, and their diagnosis of MS (Minden & Schiffer, 1993). These figures were repeated in the study by Skegg, Corwin and Skegg (1988). Research shows that patients can welcome their diagnosis (O'Connor, Detsky, Tansey & Kucharczyk, 1994), as, for many, it was a relief to know that they could dismiss "often unexpressed fears of madness, brain tumours and 'making it all up'" (W. B. Mathews,
The difficulty of the diagnosis, unpredictability of the illness trajectory, lack of a cure, and the significance of loss, make it imperative to understand the psychological dimensions of this disease. Despite the minor part it is likely to play (Ron & Feinstein, 1992), the role of stressful events in precipitating relapses is frequently reported, and adds to an image of the neurotic patient (Skegg et al., 1988). Doctors may be taught to expect that patients with mild MS may become incapacitated by non-organic symptoms and that this is possibly a form of neurosis (Boyle, Clark, Klonoff, Paty & Oger, 1991; W. B. Mathews et al., 1985). Doctors may also be taught that, although rare, MS may present with an acute onset of psychotic symptoms.

1.2.2. Psychosis

Feinstein et al. (1992b) assessed ten MS patients with psychotic illness. Compared to non-psychiatrically disturbed MS controls, there was a tendency for higher total lesion score - particularly around the periventricular areas and the temporal horn. In addition, the MS patients had a later age of onset of psychosis than in the schizophrenic population, typical of mental disorders due to a general medical condition (American Psychiatric Association (APA), 1994).
1.2.3. Euphoria
The most frequently assumed psychiatric manifestation of MS is euphoria. However, research figures vary markedly; from 0 - 84% for euphoria (Boyle et al., 1991, p. 1154), and 7% - 95% for pathological laughing and weeping (Prosiegel & Michael, 1993). Furthermore, there is no consensus as to its cause (Sanders & Van Lieshout, 1992). Euphoria could mask a major depressive episode (Burnfield, 1991), or it could be associated with the focal effects of frontal lobe white matter disease (Arnett et al., 1994).

1.2.4. Depression
At any current time, between 14% - 57% of MS patients suffer from depression (Minden & Schiffer, 1993). Different chronic medical diseases may have a distinctly different impact on quality of life (Rudick, Miller, Clough, Gragg & Farmer, 1992). Both psychological reactions and direct disease activity are implicated in the aetiology of depression in MS.

People with MS often need to deal with unpredictable (even daily) fluctuations of their symptoms. On average, 60% are unemployed within 10-15 years of onset, 40% spend most of their day alone, and 53-72% suffer significant marital discord (Minden & Schiffer, 1993, p. 36). Considering the concomitant stresses associated with the illness, many consider depression a normal psychological reaction to MS (and, as such, it is often ignored or left untreated).
However, when compared to people suffering from other medical illnesses or disabling conditions (e.g., spinal cord injury), people with MS experience significantly more affective disturbances (Minden & Schiffer, 1993). This supports the possibility that demyelination plays a significant role. Furthermore, where the disease primarily involves cerebrum lesions, then the rate of depression in MS patients is much higher than with spinal cord lesions. Other factors, such as drugs used in the treatment of MS exacerbations (Acorn & Anderson, 1990; Siblerud, 1992), can also contribute to affective disorders.

1.2.5. Depression and Cognition

Whatever the cause, depression is common in MS and may invalidate assessments of cognition (e.g., via low motivation, slowed thinking and poor concentration) (Sandroni, Walker, Tech & Starr, 1992; Minden & Schiffer, 1990a). Gilchrist and Creed (1994) ascertained depression to be associated with significant cognitive impairment. The opposite may also occur, where depression inventories can be confounded by poor cognition (e.g., reduced insight) or other MS symptoms (e.g., fatigue).

Minden, Moes, Orav, Kaplan and Reich (1990b) determined that medication has an impact on cognitive test performance. Conversely, many researchers (Rao, 1993; Ron, Callanan & Warrington, 1991) determined medications and mood disorder contributed minimally in explaining the cognitive problems found in
MS. The discrepant findings have led to differing emphasis being placed on psychiatric status and medications. Although generally, antidepressant medication is not considered grounds for exclusion (Grigsby, Ayarbe, Kravcisin & Busenbark, 1994), pharmacological influences on neuropsychological testing should first carefully be gauged. Without such an appraisal, one cannot accept the validity of test results. Besides depression and medication, fatigue can also affect cognitive ability.

1.3. FATIGUE

Fatigue, a symptom common to both depression and multiple sclerosis (Buelow, 1991; Feinstein, Kartsounis, Miller, Youl & Ron, 1992a), influences cognitive functioning. Patients with chronic fatigue syndrome also show significant impairment on tasks of complex concentration and information processing ability (DeLuca, Johnson, & Natelson, 1993). However, like depression and cognitive dysfunction, fatigue may also be due to specific lesion sites (Clark et al., 1992).

In summary, the labyrinthine interaction of these variables make a multifactorial aetiology of cognitive difficulties in MS most likely. Depression, anxiety, cognitive dysfunction and fatigue may be independent symptoms of MS. Depression, anxiety and fatigue may cause reversible cognitive symptoms, or may be secondary to, cognitive impairment. (See Diagram 1.)
1.4. COGNITIVE DEFICITS

1.4.1. Prevalence

Depending on the sample selected, figures of cognitive impairment differ markedly (Feinstein et al., 1992a; Halbreich, 1993). According to Rao, Leo, Bernardin and Unverzagt (1991a), approximately 50% - 65% of patients attending MS clinics are...
cognitively impaired. Prevalence rates for relapsing-remitting (RR) MS patients tend to be between 25% and 35%, although results have ranged from 10% to 60% (Pugnetti et al., 1993, p. S64), while up to 60% - 70% of chronic progressive (CP) MS patients show pathological results on psychometric tests. It is estimated that approximately 40% - 45% of the entire MS population have some degree of cognitive dysfunction (Grafman, Rao, Bernardin & Leo, 1991).

Although statistics differ, it is generally agreed that South Africa has a low prevalence of MS (Thornton & Lea, 1992), with 0.4 per 100 000 per annum diagnosed in South Africa (W. B. Mathews et al., 1985). Multiple Sclerosis is rare among indigenous Black people within Southern Africa and uncommon in people previously classified as "Coloured" and Indian (Dean et al., 1994).

1.4.2. Subcortical dementia and MS
Cognitive fall-off may be subtle and variable. Due to the unique nature of MS pathology, and the uncertainty regarding the effects of disseminated demyelination of white matter on cognitive function, MS patients may show atypical cognitive deficits. As these deficits may not be concordant with current conceptions of brain-behaviour relationships (Ryan et al., 1993), they may be overlooked. Although cortical atrophy in the pathogenesis of cognitive disturbance in MS cannot be completely ruled out (Pozzilli et al., 1993), it is cortical suppression or
deactivation, secondary to disconnection from subcortical structures, that remains the best current explanation for cognitive deficits in the illness (Honig, Ramsay & Sheremata, 1992).

Multiple sclerosis affects a wide array of cognitive domains, with recent memory, sustained attention, information processing speed, abstract thinking, visuospatial skills and verbal fluency frequently reported as impaired (Comi et al., 1993; Minden, 1990b; Rao, St Aubin-Faubert & Leo, 1989b). Immediate memory, recognition memory, language functions and general intelligence appear to remain relatively intact (Rao, 1993). The general consensus is that this pattern of cognitive decline in MS is a subcortical dementia, similar to the pattern of subcortical dementia found in Parkinson's Disease, Huntington Disease and progressive supranuclear palsy (Horton & Siegel, 1990; Jennekens-Schinkel, Van der Velde, Sanders & Lanser, 1990b). This differs from the cortical dementias (e.g., Alzheimer's disease) where intellectual decline is a result of amnesia, agnosia and aphasia (Rao, 1993).

1.4.3. Conflicting Results
Understanding cognitive functioning in MS is hampered by the variable research findings. For example, verbal memory impairments were found in some studies (DeLuca, Barvieri-Berger & Johnson, 1994), but not in others (Ron et al., 1991). Rao, Leo, and St. Aubin-Faubert (1989c) suggested immediate memory to be intact, while Grigsby et al. (1994) deduced immediate memory to be
impaired. Arnett et al. (1994) described definite links between frontal lobe white matter involvement and conceptual reasoning skills. However, Beatty (1993) found no convincing evidence that conceptual functions were causatively associated with frontal lobe lesions in MS patients. And while many researchers (Kessler, Cohen, Lauer & Kausch, 1992; Rao, 1993) claim general intellectual functioning to be preserved, others (Canter (1951) cited in Rao, 1986; Ron et al., 1991) found evidence of intellectual decline.

1.5. METHODOLOGICAL PROBLEMS

Discrepant findings on the cognitive nature of MS is in part due to the considerable variation in methodology and sample selection, thus hindering the pooling of data (Peyser, Rao, LaRocca & Kaplan, 1990). Biased sampling, small sample sizes, differing diagnostic criteria, inappropriate or no controls, divergent psychometric assessments, and lack of longitudinal studies, are frequent methodological flaws.

1.5.1. Heterogeneity

The most obvious difficulty in research into this illness is its heterogeneity. Symptomatology for each patient can fluctuate, and symptoms between patients can be markedly different in nature, severity and course. Biased sample selection often under-represents patients with a benign course of MS, and MS patients who are institutionalized, or unable to tolerate testing due to severe motor / sensory impairment, are seldom included in research (Rao et
1.5.2. Age and education

In many studies, subjects' ages and education are not controlled for, and few (Ryan et al., 1993) place an age limit on participants. Thus older or relatively uneducated patients could be classified as cognitively impaired when they are functioning close to their premorbid level (Rao et al., 1989a). Conversely, in highly educated subjects, performance at the norm for the general population, may be indicative of cognitive decline. Kessler et al. (1992) and Jennekens-Schinkel et al. (1990b) found highly educated subjects to have inflated performances on memory and learning tests. Similarly, socio-economic status has been attributed as a confounding factor (Minden et al., 1990b). Widespread low education and lack of standardized tests make cognitive assessment problematic in South Africa.

1.5.3. Control groups and longitudinal studies.

Multiple sclerosis is a unique neurological disorder, and its fluctuating, unpredictable nature makes it difficult to find an ideal comparison group. Consequently, in most research into MS and cognition, there is a conspicuous lack of control groups. If controls are used, then elementary sensory and motor requirements, psychiatric status and medication should ideally be controlled for, both within and between groups. However, the most appropriate investigation into cognitive impairment is the longitudinal study.
Few longitudinal studies exist (Jennekens-Schinkel, Laboyrie, Lanser & Van der Velde, 1990a; Mariani et al., 1991). Seldom can a direct comparison be made between a patient's premorbid and postmorbid test performance, and decline must be based on assumptions of premorbid functioning. Canter (1951) (cited in Rao, 1986) obtained the Army General Classification Test intelligence scores for 32 males who were healthy at the time they entered the military, but later developed symptoms of MS. Readministered approximated four years later, the same test revealed a mean drop of 13.5 intelligence quotient (IQ) points.

The predominant failing of most longitudinal studies, has been their small sample size (Arnett et al., 1994; Feinstein, Ron & Thompson, 1993). Even when practice effects are taken into account, the natural history of cognitive deficit in MS is highly variable, and in fact, improvement over time is possible.

1.6. FACTORS PREDICTIVE OF COGNITIVE DYSFUNCTION IN MS

It remains uncertain what factors are predictive of cognitive dysfunction in multiple sclerosis. Factors such as duration of the illness, degree of physical disability and type of MS have been extensively researched to determine their impact on cognitive functioning.

1.6.1. Duration of the illness

Many researchers have concluded that the cognitive symptoms in MS
do not appear to be linked with duration of the illness. Significant dementia can occur early on in the disease (W. B. Mathews, 1979; Ron et al., 1991) even before there are sufficient neurological symptoms for a diagnosis (Rao, 1993). However, other research has associated cognitive dysfunction with an advanced disease state (Ron et al., 1991; Smith et al., 1993).

1.6.2. Degree of physical disability
Several studies (Kessler et al., 1992; McIntosh-Michaelis et al., 1991) have determined cognitive impairment to be associated with physical disability. Conversely, Beatty, Goodkin, Hertsgaard and Monson (1990a) did not find physical disability to be related to cognitive performance, and patients with only minimal physical impairments can have cognitive dysfunction severe enough to limit daily activities significantly (Beatty & Goodkin, 1990b). The gravity of physical disability should not be underestimated. Severe motor, sensory and visual deficits can interfere with the validity of certain neuropsychological tests, and fatigue and pain can result in problems with attention and memory.

1.6.3. Type of MS: Relapsing-remitting versus chronic progressive
When compared to healthy controls, even people with mild MS, and MS in remission still tend to have some cognitive dysfunction (Klonoff, Clark, Oger, Paty & Li, 1991). However, often it is only with sophisticated neuropsychological tests that such impairment can be detected in functionally independent RR MS patients (Ryan et
al., 1993). In their study of 41 MS patients with mild overall functional impairment, Anzola et al. (1990) established very mild cognitive impairment. By selecting patients with a RR course of MS, they may have excluded the majority of patients with MS-related dementia. Pugnetti et al. (1993) concluded the typical prevalence of cognitive impairment in RR patients to be about 31%.

Some research suggests that the chronic-progressive course in MS produces more cognitive symptoms than the RR course (Comi et al., 1993; Kessler et al., 1992; Mariani et al., 1991). But these findings have been unsupported by other researchers (Beatty et al., 1990a; Jennekens-Schinkel et al., 1990b). While research findings differ, it is also suggested that cognitive impairment in MS is strongly associated to the amount of cerebral involvement on Magnetic Resonance Imaging (MRI).

1.7. ADVENT OF NEUROIMAGING TECHNIQUES

In recent years, due to the advent of sophisticated neuroimaging techniques, the in vivo evaluation of lesions is now possible. Since 1981, the MRI has contributed to the diagnostic certainty of the disease (Goodkin, Rudick & Ross, 1994).

Again, research is troubled by differing methodological approaches. Anatomical markers and interresearcher procedures are unstandardized (Swirsky-Sacchetti et al., 1992). Field strengths in MRI magnets differ, as do evaluations of brain MRI films (Comi
et al., 1993). Most methods of quantifying lesions have only been crude approximations (Ron et al., 1991), and there are differing methods of estimating lesion volume (Feinstein et al., 1992b). Despite these limitations, the MRI remains a sensitive tool for in vivo evaluation as direct evidence of disease activity can be monitored without invasive procedures.

1.7.1. Magnitude versus spread of lesions

Global cognitive deterioration is often associated with Total Lesion Area (TLA). It is generally postulated that if the minimum TLA ranges from 20 - 30 square centimetres, then cognitive dysfunction is more likely to occur. Izquierdo, Campoy, Mir, Gonzalez and Martinez-Parra (1991) found patients with MRI lesions over 2000 square millimetres in the periphery of the lateral ventricles, to perform significantly worse on tests of memory, learning and acquisition. Arnett et al. (1994) also determined 20 square centimetres to be significant. On the more conservative side, Ron et al. (1989c) established the significant TLA to be 30 square centimetres. And Swirsky-Sacchetti et al., (1992), ascertained TLA for their cognitively impaired group to average 28.30 square centimetres, whereas for the unimpaired group, the mean was 7.41 square centimetres.

Depending on their location, some focal lesions can result in specific cognitive and neuropsychiatric deficits (Prosigiel & Michael, 1993). Even early in the disease, selective cognitive
deficit can result from lesions which happen to interrupt fibre tracts subserving specific functions (Comi et al., 1993). It is likely that both volume and location of MS lesions can play significant roles in cognitive function, and that an interplay between the two is the most likely.

1.8. THE MRI AND COGNITIVE SYMPTOMS

Since 1987, MRI lesions have been correlated with neuropsychological impairments (Goodkin et al., 1994), providing new insight into the pathogenesis of cognitive dysfunction in MS. Commonly, TLA, lesion location, ventricular dilatation and regional changes in cerebral physiology are determined in correlating MRI brain changes with cognitive test performance (Rao, 1993). In other studies, summed length of the individual plaques' longest diameters (Ron et al., 1991), and left versus right hemispheric involvement (Anzola et al., 1990) are used.

Overall lesion burden tends to be associated with cognitive deficit, periventricular lesions with verbal memory deficits, bilateral hippocampal lesions with recent memory difficulties (Rao, 1993), and prefrontal cortex atrophy can be associated with working memory difficulties (Grigsby et al., 1994). Arnett et al. (1994) associated frontal lobe lesions with conceptual reasoning deficits and perseverative responses.
1.8.1. The corpus callosum and interhemispheric disconnection

Characteristically, MS patients have corpus callosal involvement. The corpus callosum (CC) is a prominent band of compact white matter and the major axonal commissure of the brain, connecting the two cerebral hemispheres (Georgy, Hesselink & Jernigan, 1993). Sustained attention, mental processing speed and rapid problem solving are dependent on precisely timed interhemispheric communication (Goodkin et al., 1994; Rao et al. 1989a), and thus MS is a particularly useful model of interhemispheric disconnection (Schnider, Benson, & Rosner, 1993). Pelletier et al. (1993) proposed the CC could play a role in cognitive and behavioural impairment, and Rao's (1993a) described slowed word naming if items were in the left visual field.

Recent evidence exists for sex- and handedness-related variations in callosal size (Pozzilli et al., 1991a). Georgy et al. (1993, p. 949) reported that in some research there is a larger main callosal area in men, and an 18-28% increase in the main callosal area in persons with right hemispheric cerebral speech dominance. However, Pelletier et al. (1993) determined no significant effect or interaction on these variables. Sex- and handedness-related variations remain controversial, and as yet it is not known how this affects people with MS.

1.8.2. Ventricular dilatation

Dilatation in MS generally relates to demyelination (i.e., atrophy)
of the surrounding white matter, and reflects pathological changes in the periventricular regions. Thus evaluating the degree of ventricular dilatation should be an important variable in all MRI research into cognitive symptomatology.

Ventricular dilatation disrupts periventricular pathways interconnecting prefrontal and limbic structures which may explain memory and conceptual reasoning deficits. Comi et al. (1993) (N=100) ascertained ventricular dilatation and CC atrophy to be correlated significantly with low scores on almost all the neuropsychological tests. In patients with extensive, irregular, periventricular demyelination, Mariani et al. (1991) found a relatively inferior performance on concept formation, non-verbal reasoning and verbal memory tests when compared with controls. Periventricular and frontal lesions have also been associated with "psychologic symptoms" (i.e., depressed or euphoric mood, irritability, reduction of drive and disorder of judgement) (Reishies, Baum, Brau, Hedde & Schwindt, 1988).

1.9. SUBJECTIVE EXPERIENCE OF COGNITIVE FUNCTIONING
Very few MS studies (DeLuca et al., 1993; R. Taylor, 1990) have looked at MS patients who subjectively feel that they suffer cognitive symptomatology. Metamemory which refers to a person's knowledge about their memory (Beatty, 1993), is an indication of how accurately judgements about one's own memory can be made.
Grigsby et al. (1994), determined patients' complaints to be congruent with their psychometric test findings.

However, Beatty and Monson (1991) established that MS patients tended not to acknowledge test-demonstrable memory deficits, and concluded that patient self-reports on memory were likely to be unreliable sources of information. And, McIntosh-Michaelis et al. (1991), found subtle cognitive changes tended to go unrecognized by people with MS, their families or clinicians. It may be that patients with moderate to severe cognitive dysfunction may be apathetic and loose insight and self-awareness, thus under- or over-reporting cognitive symptoms. Alternatively, patients may be threatened by cognitive decline, and deny that it is happening.

Unfortunately, there remains a dearth of research into the area of subjective experience of cognitive deficits. Gilchrist and Creed (1994) determined that patients repeatedly emphasized the discrepancy between their subjective experience of cognitive impairment and the lack of such disability evident to others. Especially when cognitive symptoms were variable or unpredictable, patients can be labelled as "lazy" or "lacking motivation" (1994, p. 200), often causing familial strife.

1.10. AIMS OF THIS STUDY
This study investigates ten people with MS who feel they have cognitive difficulties because of their MS. It aims to:
1.) Explore the subjective experience of cognitive deficits, as this is frequently ignored in research.

2.) Investigate the presence of psychological distress in the group, as depression and anxiety are frequently associated with the illness.

3.) Assess whether or not there is evidence of cognitive deficits, and if there is, if it fits the pattern of a subcortical dementia.

4.) Determine whether their MRI scans replicate the patterns of atrophy frequently reported in cognitively compromised MS patients.

Neuropsychological tests, psychiatric and personality inventories, and MRI investigations were done on each participant to evaluate the exact nature of their cognitive deficits (if any). In anticipation that confounding aetiological variables may exist, it is intended that all the participants will be re-assessed at 5-yearly intervals, in order to have a longitudinal representation of their course of cognitive dysfunction and MS.

This study does not aim to establish differences between people with MS and controls (as there is no ideal comparison group). Rather, it seeks take a descriptive look at cognition and emotional well-being of ten people who subjectively experience cognitive deficits due to their MS, and how this evolves over time.
Chapter Two

**METHODOLOGY**

2.1. SUBJECTS

A letter was sent out with the South African National Multiple Sclerosis Society (SANMSS) newsletter explaining the research and requesting participants. People who, firstly, believed they suffered from cognitive symptoms, and secondly, that these were due to their MS, were asked to respond. Forty people replied and were initially screened by telephonic interview. The following exclusion criteria were applied:

1. No subject fifty years or older was included in the study.
2. No subject had impairments of sight, hearing or motor function of sufficient severity to preclude valid testing.
3. No subject was currently a medical or psychiatric inpatient.
4. All subjects were fluent in English.

Some people wanted to talk about MS and cognition, but were unwilling to be assessed (N=4), and nine respondents were over 50. One person, actively suicidal, was referred on to her doctor for a psychiatric referral. Eleven people were provisionally accepted into the study. However, one subject had a law suit pending, and wanted her neuropsychological test results to be used as evidence.
As this could have been interpreted as an invested bias, she was excluded from the research after the initial interview and screening measures.

The ten subjects (six women, four men), ranged in age from 27-47 years. (See Table 1.) Onset of MS symptoms ranged between two and 19 years, with a mean of 7.3 years since clinical diagnosis. One subject was wheelchair-dependent, and three were dependent on walking aids. All were right-handed. Years previous to the study, one subject had had meningitis, one a pulmonary embolism which had required resuscitation, and another, two myocardial infarctions. Only one subject has a history of loss of consciousness (four hours), with no post-traumatic amnesia reported.

Six subjects described a RR, and four a CP course. One subject with RR MS had had an exacerbation three weeks prior to his assessment. At the time of testing, three subjects were on Prozac (Fluoxetine), one was on Tegretol, one on Tenormin (Atenolol), and one subject was on Dormican (Midazolam) at night.

The mean years of education was 16.1. Two of the subjects were medical specialists, and four were secretaries or clerks. Half the sample were self-employed (estate agency, picture framing, computing) or assisted a spouse / partner. Of the six professionals, two no longer worked in their area of discipline, and three had had to make adjustments in their initial job
description in order to accommodate their symptoms. Nine subjects were "White" and one "Coloured".

Table 1.

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</tr>
<tr>
<td>10</td>
<td>47</td>
<td>M</td>
<td>Insurance</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td></td>
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</tr>
</tbody>
</table>

\[ \bar{X} = 37.2, \quad SD = 6.7 \]

<table>
<thead>
<tr>
<th></th>
<th>16.1</th>
<th>12.7</th>
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<tbody>
<tr>
<td></td>
<td>4.4</td>
<td>5.4</td>
<td>4.6</td>
</tr>
</tbody>
</table>

2.2. PROCEDURE

Option to withdraw at any time was agreed upon prior to outset, and feedback and explanation of individual results were offered. All the subjects gave informed consent and permission to contact their neurologists. Subjects were agreeable in principle to being re-assessed in five yearly intervals for a long-term follow-up study.
Frequently, fatigue interferes with the functional status of MS patients, and in cognitive assessments. Rao, Leo, Haughton, St. Aubin-Faubert and Bernardin (1989a), and Arnett et al. (1994) emphasized the need to limit the length of testing sessions. To minimize fatigue, the assessment took place over three testing sessions, with each session taking approximately two hours. Subjects were encouraged to take breaks when tired. The second and third sessions were all arranged to take place within one week of the participant's MRI investigation. Mariani et al. (1991) emphasize the need for the minimum of delay between the MRI and neuropsychological assessments as MRI modifications may not be associated with clinical evidence.

All subjects underwent further screening measures (also used for analysis), a neuropsychiatric interview, an assessment of anxiety and dysthymia, neuropsychological testing and MRI investigations. After the completion of the first neuropsychological battery, one subject left the study due to distressing family problems. The neuropsychological tests were scored, with the researcher blinded to the MRI results.

2.3. Screening Questionnaires
During the first interview, the following screening measures were administered: the Rey Fifteen Item Test; the Mini Mental State Examination and the Hamilton Rating Scale for Depression. The Rey
Fifteen Item Test (RFIT), may be used to assess the presence of a pseudoneurological memory disorder or malingering (Walsh, 1990). The Mini Mental State Examination (MMSE) is a brief screening measure for dementia (Folstein, Folstein & McHugh, 1975), and served to exclude subjects too cognitively impaired to give informed consent. The standard cutoff of 24/30 was used.

The Hamilton Rating Scale for Depression (HRS) was completed to exclude subjects with depression. Although the HRS is not a diagnostic instrument for depression (Hamilton, 1967), it measures mood and all the vegetative symptoms of a clinical depression. In a longitudinal study it is useful in measuring symptomatic changes over time. Research on non-psychiatric populations (Schwab, Bialow, Clemmons & Holzer, 1967) demonstrated that a score of 43/100 for questions one to 17, correlated with the Beck Depression Inventory (BDI) and with other depression criteria. In this study, a conservative cutoff score of 30 (for questions one to 17) was used as a screen for clinical depression. In summary, the following cutoff scores and screening measures were implemented at the first interview:

5.) Cutoff score of 24/30 on Mini Mental State Examination.
6.) Cutoff off 30 on the Hamilton Rating Scale for Depression.
7.) No signs of malingering in the Rey 15 Item Test.
2.4. THE NEUROPSYCHIATRIC INTERVIEW

Interviews took place at the subjects' homes, and were based on a structured and semi-structured questionnaire (see appendix). The questionnaire examined personal and family history of neurological and psychiatric illness, and the subjects' subjective experience of cognitive function. Questions exploring the subjects' definitions of "cognitive", what symptoms they experience, why they relate it to their MS, and how they compensate, were included. Their perception of family members' and neurologists' reactions to their "cognitive" symptoms were also recorded. Direct quotes from open-ended questions were used to provide additional information.

2.5. NEUROPSYCHOLOGICAL TEST BATTERY

In this research, tests of general intelligence, attention, memory, language, abstract and reasoning ability, and handmotor dexterity were included, as these cognitive domains have shown to be compromised in MS.

2.5.1. Tests of General Intelligence

Subjects completed the South African Wechsler Adult Intelligence Scale (SAWAIS). Comi et al. (1993) detected 37% of MS patients (N=100) to show decline in intelligence. However, visual and motor impairment (common in MS), can negatively influence test results. This particularly applies to the performance subtests, making the Performance Intelligence Quotient (PIQ) susceptible to
deterioration. In contrast, the Verbal Intelligence Quotient (VIQ) is relatively resistant to impairment in MS (Ryan et al., 1993). Thus VIQ is often used as an index of global cognitive performance (Arnett et al., 1994), especially when MS patients have visual or motor impediments. For this reason, the VIQ and the Full Scale Intelligence Quotient (FSIQ) were compared to each other, as was PIQ with VIQ.

All the SAWAIS subtests were administered, except for the Vocabulary subtest, due to time constraints. Age-scaled standardized scores for each subtest were obtained. In Digit Repetition (DR), Digits Forward (DF) and Digits Backward (DB) were viewed as separate tests, as they involve different mental activities and are affected differently by brain damage (Lezak, 1983). The difference between DF and DB, Digits Difference (DD), should not be greater than two (Lezak, 1983).

2.5.2. Tests of Attention

Attention difficulties are often implicated in MS, whether due to anxiety, depression, fatigue or cognitive dysfunction. Digits Forward (SAWAIS), commonly assumed to be a test of memory, is more closely related to the efficiency of attention, or a test of the "passive span of apprehension" (Hayslip & Kennelly, 1980, cited in Lezak, 1983). The Visual Memory Span (VMS) of the Wechsler Memory Scale-Revised (WMS-R) is a sequential block-tapping task which is
considered a visuo-spatial equivalent of DR (SAWAIS) (Anzola et al., 1990). Digit Repetition tends to be more vulnerable to left hemisphere involvement (Lezak, 1983), and VDS more susceptible to right hemisphere damage. In this way, by comparing DF (SAWAIS) with visual DF (VMS, WMS-R), lateralization of function to the right and left hemispheres, is possible.

Originally part of the Army Individual Test Battery, the Trail Making Tests (TMT) function as tests of attention, visuomotor tracking, coordination, visual scanning, motor speed, and double conceptual tracking (working memory). Because the TMT requires cognitive flexibility, it is highly vulnerable to brain damage (Lezak, 1983). The TMT is a paper and pencil test. In TMT-A, the participant connects 25 consecutively numbered circles randomly distributed on a sheet of paper, as rapidly as possible. In TMT-B, the participant alternatively connects the numbers and letters (C. G. Mathews et al., 1970). Percentile ranks for TMT-A and TMT-B were extrapolated from Lezak (1983) (Spangenberg, 1992).

2.5.3. Memory
Memory is reportedly the most common cognitive symptom affected by MS (Burnfield, 1993) and memory tests, frequently applied to people with MS, were included in the battery.
2.5.3.1. Tests of Prospective and Episodic Memory
People with MS often complain of forgetting tasks that other people have asked them to do (Burnfield, 1993), therefore prospective memory was assessed. At the beginning of the neuropsychiatric interview, subjects were asked to remember to do three things at the end of the interview (to comment on the weather, to pick up a coin, and to undo a button/sleeve). If subjects failed to remember this spontaneously, they were prompted. Subjects were also asked four episodic memory questions (e.g., "What did you eat last night for supper?"; "What was on the news?"; "What did you wear yesterday?").

2.5.3.2. Tests of Working Memory
Working memory, the temporary storage and processing of information necessary for the concurrent performance of a wide range of cognitive tasks (Baddeley, 1992), was assessed on Serial Sevens (MMSE), TMT-B, Visual Digits Backward (VDB) (VMS, WMS-R), DB (SAWAIS). Norms for VDB (VMS, WMS-R) were taken from the WMS-R manual (Wechsler, 1987). Lateralization of function was again looked for in comparing Visual Digits Backward (VMS, WMS-R) with DB (SAWAIS).

2.5.3.3. Tests of Auditory Memory
In their research on cognitive function in MS, Pozzilli et al. (1991b) found the Rey Auditory Verbal Learning Task (RAVLT) to be the most sensitive test to elicit memory deficits. This test
assesses verbal learning, delayed recall and recognition memory (Gilchrist & Creed, 1994). Subjects listen while 15 words (List A), are read to them, and thereafter repeat as many as possible. Five repetition trials are allowed.

Trial I subtracted from Trial V represented the number of new words learned over the five trials. Norms for trials I to V were taken from Wiens, McMinn and Crossen (1988). Normally, people learn five words over the five trials (Savage & Gouvier, 1992). Multiple sclerosis patients have tended to perform relatively poorly on the first trial, but maintain a normal learning curve (Minden et al., 1990b).

An interference trial (List B) is given after Trial V. In error, in this research, the recognition trial was administered immediately after the five repetition trials. In the recognition trial, subjects must identify the List A words embedded in a list of distractors. Normally in most neurological illnesses, patients' recognition memory is relatively spared (Binder, Villanueva, Howieson & Moore, 1993). Half an hour later, a delayed free recall test was administered.

Two other auditory memory tests were administered. In Logical Memory (LM), a short story was read and then immediate recall tested. The delayed recall score was the percent of material retained from the initial recall after a 30 minute delay. A South
African version of LM used clinically, based on the WMS-R, was used, and the story was scored on the same criteria as the WMS-R (Wechsler, 1987). **Digit Supraspan** (DSS) was measured by the number of trials taken for a participant to correctly produce a series of digits one longer than their longest string on the DF (SAWAIS), on two consecutive trials (Zangwill, 1943). A maximum of ten trials was allowed.

2.5.3.4. Tests of Visual Memory

Visual equivalents of the auditory memory tasks were applied. A new test, the **Hopkins Board of Visual Recall** (HBVR) was administered, to assess visuospatial memory and learning. The Hopkins Board is equally divided into nine squares and subjects must recall which of nine different pictures belong to which square. A maximum of ten trials is allowed for, in which subjects must obtain two consecutively correct trials. Like the RAVLT, the HBVR consists of learning trials, a 30 minute delayed recall, and a recognition task. The recognition task was designed for this research, and subjects had to identify the original pictures, which lay embedded amongst pictures of similar shape or function. Currently, no percentiles are available, but in a group previously studied, the mean to criterion was 6.4 trials (De Villiers, 1993).

**Visual supraspan** (VSS) was also measured, i.e., the number of trials needed to tap out a block longer than their longest forward tapping sequence on VMS (WMS-R). This was compared with Digit
The Rey-Osterrieth Complex Figure (ROCF) was designed by Rey to assess perceptual organization and visual memory in brain-damaged patients (Rey, 1941, cited in Lezak, 1983), and is used extensively as a neuropsychological test (Rosselli & Ardila, 1991). The subjects were presented with a complex, multi-component geometrical drawing (Pozzilli et al., 1991b), and required to copy it. As executive functions are often implicated in MS (Beatty, 1993), special attention was paid to the way the figure was copied, and subjects used consecutively different-coloured pens to complete the figure. In this way, the participant’s ability to conceive, organize and execute a plan, were assessed.

Three minutes after the copy task, and after interference, subjects reproduced it from memory. E. M. Taylor’s (1959) scoring system, adapted from Osterrieth (1944) was used (cited in Lezak, 1983). Results were compared with percentile norms adapted from Osterrieth (1944) (cited in Lezak, 1983) by Lezak (1983). The ROCF was also used as a means to detect praxis alterations (Izquierdo et al., 1991).

As an extension of the Digit Symbol subtest (SAWAIS), Digit Symbol Incidental Recall (DSIR) was used as a test of incidental visual recall (Kaplan, Goodglass & Weintraub, 1978, cited in Lezak, 1983). Subjects were not warned that on the completion of the subtest,
they would be required to recall the symbols representative of the nine numbers. A recall of seven out of nine, is considered the low end of average for normal persons (Lezak, 1983).

2.5.4. Tests of Language Ability

In MS, many patients complain of not being able to find words which remain at the 'tip of the tongue'. The Renfrew Word Finding Vocabulary Scale (RWFVS) is a measure of naming skill (i.e., dysnomia) and word retrieval ability. Subjects were presented with 59 graded pictures (from "cup" to "castor") to name. Inability to name an object, and substitutions (e.g., "it scares birds away" instead of "scarecrow") were scored. There are no adult norms available.

Subjects were also given two verbal fluency tasks, as many MS patients have difficulty in the speed and ease of verbal production (Rao, 1993). The Controlled Oral Word Association Test (COWAT) assessed the timed production of words after phonemic (C, F, and L) cues. Scores were adjusted for age, sex and education, and norms taken from Lezak (1983). Subjects were also presented with semantic cues (towns and animals). Typically, semantic cued word associations are easier than phonemic cues (Lezak, 1983), and in clinical practice, people normally obtain 15 words per semantic category in one minute.
2.5.5. Tests of Abstract and Reasoning Ability

Poor performance on the Wisconsin Card Sorting Task (WCST) has been used as an indicator of frontal lobe dysfunction (Beatty & Monson, 1991). The WCST assesses a variety of higher cognitive abilities (e.g., abstraction, rule learning, concept formation, conceptual reasoning and cognitive set-shifting) (Mendozzi et al., 1993). It consists of a set of stimulus cards and the subject is required to sort them according to one of three attributes in turn (colour, shape and number) (Heaton, 1981). As in previous studies in MS (Callanan, Logsdail, Ron and Warrington, 1989; Ron et al., 1991), a shortened version of the WCST is used. As with Minden et al. (1990b), the test was terminated after 64 cards were placed, three trials achieved, or 50 cards placed without attaining one sort. For a normal population, the total number of (any) errors to learn the first category, is 13.4 (Heaton, 1981).

2.5.6. Tests of Handmotor Dexterity

Neuropsychological batteries on MS must of necessity include tests to determine the effects of slowed handmotor functions and dexterity. Not to do so, would implicate the validity of other timed tests such as Trail Making and Digit Symbol (SAWAIS). The Grooved Pegboard Test (GPT) is a manual dexterity task (C. G. Mathews & Kløve, 1964). The GPT is a metallic board, four inches square, with five rows of five holes, each with a differently positioned slot, and the patient (using one hand at a time) must
fill each slot, horizontally in order, as quickly as possible (Kessler et al., 1992). In order to be inserted accurately, the pegs must first be rotated properly. A cut-off time of five minutes is allowed for.

Compared to most pegboards, this test requires more complex visual-motor co-ordination. Some research (Kessler et al., 1992) found the GPT successfully predicted performance on a number of memory tasks. Norms were based on the manual produced by Lafayette Instrument Company (1989).

2.6. ASSESSING ANXIETY AND DYSTHYMIA

Given the frequent reports of depression and anxiety in MS, and given that they may influence neuropsychological test results, it is of fundamental importance to assess the psychiatric status and psychological well-being of the subjects.

Subjects completed the Millon Clinical Multiaxial Inventory (MCMI) - II personality inventory. The MCMI-II investigates a wide range of psychopathology, whether long-standing, acute or symptomatic clinical syndromes (Wetzler, 1990). The MCMI was originally not designed for, nor standardized on non-psychiatric populations, but a Base Rate Score (BRS) of 35 is expected as the median score for "normal" or nonpsychiatric populations (Choca, Shanley & Van Denburg, 1992). However, research has shown that normals can score
on pathological levels (i.e., elevations of 75 and over), implying overpathologization of certain personality features (Wetzler, 1990, p. 458). For this reason, specific attention was paid to the scales of Anxiety, Dysthymia, and Major Depression, and not to personality profiles.

The MCMI-II was selected because, besides long-standing syndromes, it is sensitive to clinical states (e.g., anxiety) which fluctuate over time (Wetzler, 1990). In this way the MCMI is an excellent tool to pick up the degree to which mood state can affect a person's cognitive test performance.

Finally, subjects completed the General Health Questionnaire (GHQ) which measures anxiety, social dysfunction, somatic complaints and depression (Acorn & Anderson, 1990), and has been used in MS research (Ron et al., 1991). Subjects score changes over the previous weeks ("much worse than usual", "worse than usual", "same as usual", or "better than usual"). While no cutoff point was employed in this research, the GHQ was used as a measure of acute changes or chronicity in mental health and attitudes.

2.7. MRI INVESTIGATIONS
Magnetic Resonance Imaging studies were performed with a superconducting (version 5.5) Tesla magnet (Elscint Unit with Gyrex V.D.L.X.). In all cases, axial and sagittal planes, with a spin
echo sequence (SE) of 2600 / 20 and SE 2600 / 90 were used. After the first two subjects, coronal SE 2600 /20 and SE 2600 / 90 were added. Proton density (PD) and T2 imaging were used to score the plaques. The summed diameter of all the plaques – or total plaque diameter (TPD) – and total number of lesions (TNL) were calculated.

These results were also scored for the right versus the left hemispheres; right and left hemisphere's total plaque diameter (RPD and LPD), and the number of lesions (RNL and LNL). The degree of CC atrophy and the degree of ventricular dilatation were scale-scored as shown in Table 2. A note was made as to whether plaques occurred in the brain stem. Although neuropsychology is generally little concerned with the brain stem (Walsh, 1990, p. 52), lesions here can affect the patient's ability to concentrate if the level of arousal is impaired.

If subjects had previous MRI material available, then comparative assessments were made. Each subject's MRI scan was examined and scored by a neuroradiologist, who was blinded to the test results. Attention was paid to the degree of ventricular dilatation, corpus collasol atrophy, and total accumulative plaque diameter. This was compared with the MRI findings from other research on cognitively impaired MS subjects.
TABLE 2

BRAIN MRI SCORING CRITERIA

(a) Degree of corpus callosum atrophy / ventricular dilatation (cerebral atrophy)

score 0 = no atrophy
score 1 = mild atrophy
score 2 = mild to moderate atrophy
score 3 = moderate atrophy
score 4 = moderate to severe atrophy
score 5 = severe atrophy

(b) Site of corpus callosum atrophy

score 0 = no atrophy
score 1 = anterior
score 2 = body
score 3 = posterior
score 4 = whole of CC showing atrophy

2.8. ANALYSIS OF DATA

Small sample size (only eight people had MRI scans), placed limitations on the way the data could be statistically analyzed, with the probability of obtaining a Type II error very high (Howell, 1989). For this reason, there was a concentration on descriptive statistics.

As no control group was employed, where possible the performance of each participant on each neuropsychological test was compared with normative data. The most relevant normative data was selected, and in some instances, age- and education-related norms were available. Subjects's scores on individual tests were converted to percentile ranks, and compared with their general intelligence (also scored as
percentiles). While general impairment can be defined as a score at or below the fifth percentile of age- and education-matched controls (Beatty & Goodkin, 1990b), here impairment was based on self-comparison to general intellectual function. In this way, effects of age and education were also accounted for.

When the median differed markedly from the mean, individual subjects' scores were investigated. Qualitative analysis of the interviews provided deeper insights into the subjective experience of the subjects.
Chapter three

RESULTS:

The interplay between MS, depression, anxiety, and fatigue on cognition is complex. The subjects, volunteering on the basis that they had cognitive deficits due to MS, were beset with doubt. Many expressed a 'need to know' whether or not their self-perceived cognitive symptoms were objectively there, and whether or not they could confidently attribute them to MS.

3.1. THE NEUROPSYCHIATRIC INTERVIEW

3.1.1. Uncertainty

"I still doubt myself. I need to know it's legitimate and I'm not just playing games. I need to know if others are feeling this way."

Subjects identified many reasons for their uncertainty, but often struggled to express themselves. Many used unique metaphors: "there's a space between me and the meaning of the word"; "a sluggishness of thinking. There isn't crispness"; "I have to scrub my brain to get it to work properly"; "it feels muddy"; "my mind feels like a train with squeaky wheels".

"I can't help thinking what connection it has with Alzheimer's, and then I think, 'Don't be ridiculous'."
The concept of MS-caused cognitive symptoms was upsetting and threatening; "Not walking is one thing. But cognition! ... [It's] too horrific!". Many actively avoided confronting their self-perceived cognitive deficits. Those who worked at home tended to be in non-intellectually demanding employment, and admitted that this made them feel safe: "I've always used my brain. Now as a housewife I'm not being tested; [it's] tucked away enough that it won't be revealed". One woman had left two jobs because she "felt [she] was letting the company down because [she] was forgetting things ... would have caused the company a lot of embarrassment". One subject abandoned her masters research owing to anxiety that she could no longer "make it". Another refrained from starting her own company because it meant people would then rely on her. They could understand that employers lost trust in them and they lost trust in themselves.

This lack of trust and self-doubt was exacerbated by the disbelief of relatives or medical practitioners, making them feel they were "frauds" and "neurotic". While all had been told of the possibility of paralysis, none had been told of the possibility of cognitive symptoms. Even those who had directly asked had been told "not to worry", and MS "only affected the white matter so it couldn't cause intellectual problems".

Those that complained of cognitive symptoms had usually been told it was depression or stress. Problems they associated with
cognitive difficulties were easily attributed to "laziness" or "manipulation", or being "mal" [mad], causing family and occupational strife. Many of the subjects had experiences of vehemently denying conversations or decisions they had made, only to be proved wrong. In turn, this led to feelings of humiliation, shame, vulnerability, lack of confidence, and "feeling stupid". Uncertainty resulted in a tendency to dismiss or laugh off the symptoms as "quaint". Many felt they avoided dealing with the threat by "covering up" their mistakes (with witticisms, humour, down-playing etc.). One felt he not only convinced others there was nothing wrong, but sometimes "fooled" himself into thinking there was nothing to worry about.

3.1.2. Confirmation

"I began to read about cognitive symptoms in [MS] newsletters. I felt triumphant, like 'I told you so!' I felt like going to the medical doctors and shoving it under their noses, to say 'You see? I was right! It wasn't in my mind!"

All subjects had found out about the possibility of MS causing cognitive symptoms through multiple sclerosis societies, self-education, or talking to other people with MS. In many cases, subjects believed it was merely confirmation of an idea "already realized". For many it was "comforting" and "reassuring" to know that they had not "made things up" or were not accountable for certain behaviours and decisions. Along with the relief were
feelings of sadness; "it was another thing the illness was taking away". All expressed fear at their experienced and anticipated potential cognitive losses, and although they wanted it "to be proved", they felt they "desperately did not want it to be true".

All subjects believed that MS could cause cognitive deficits as all had at times experienced MS-caused cognitive deficits, with eight of the ten believing their memory had been affected.

"I forget I've got something in the oven. Even if I'm standing next to the stove, I can't understand what's burning."

Other volunteered examples were: loosing track in conversations; inability to maintain concentration when reading; feeling "unable to understand"; being "muddled"; "confused" and "slow"; feeling disinhibited; having a "short fuse"; becoming "easily upset and angry". Several factors were associated with these symptoms becoming more severe: fatigue; MS exacerbations; worry; stress; extremes of temperature; and being confronted with complex material.

Subjects employed several "tricks" to help themselves. Most were avid list-keepers, kept diaries, checked and re-checked work, aided their memory through means of association and repetition, and depended on friends and family to remind them.
3.2. SCREENING MEASURES

The screening measures were also used for analysis. (See Table 3.) Subjects performed normally on the MMSE, showing no or minimal signs of cognitive decline. Subjects scored low on the HRS, and had few (if any) clinical signs of depression.

Table 3

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE (N=10)</td>
<td>28.3</td>
<td>1.252</td>
<td>26 - 30</td>
<td>30</td>
</tr>
<tr>
<td>HRS (score doubled) (N=10)</td>
<td>14.2</td>
<td>6.215</td>
<td>6 - 26</td>
<td>102</td>
</tr>
</tbody>
</table>

3.2. PSYCHO-SOCIAL INDICES

Formal indices of major depression (on the HRS and the MCMI-MDE) were low. The GHQ indices were insignificant and non-contributary. In contrast, the MCMI-II scores were elevated for both anxiety and dysthymia. (See Table 4.) Eight subjects had elevated scores (over 75) for dysthymia, and six for anxiety. The mean score was above 75 for both the Dysthymia and Anxiety scales. When the one outlier score was removed, the means rose dramatically.

Individual and familial histories revealed a marked degree of psychiatric distress and treatment. (See Table 5.) All the subjects had, in the past, either considered suicide, or considered themselves "seriously depressed", and seven subjects had sought professional help for depression. More than half the subjects
described themselves as currently depressed or were taking anti-depressant medication. Atypically, more than half the subjects had family histories of suicide (N=4), alcoholism or depression.

Table 4

TESTS OF PSYCHOLOGICAL WELL-BEING:

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHQ (N=10)</td>
<td>5.1</td>
<td>5.195</td>
<td>0 - 17</td>
<td>28</td>
</tr>
<tr>
<td>GHQ-Anguistry (N=10)</td>
<td>1.0</td>
<td>1.155</td>
<td>0 - 3</td>
<td>7</td>
</tr>
<tr>
<td>GHQ-Social Dysfunction (N=10)</td>
<td>1.5</td>
<td>1.900</td>
<td>0 - 6</td>
<td>7</td>
</tr>
<tr>
<td>GHQ-Somatic Complaints (N=10)</td>
<td>2.0</td>
<td>2.357</td>
<td>0 - 7</td>
<td>7</td>
</tr>
<tr>
<td>GHQ-Depression (N=10)</td>
<td>0.6</td>
<td>0.843</td>
<td>0 - 2</td>
<td>7</td>
</tr>
<tr>
<td>MCMI-II: MDE (N=9)</td>
<td>61.9</td>
<td>7.737</td>
<td>47 - 76</td>
<td></td>
</tr>
<tr>
<td>MCMI-II Dysthymia (N=9)</td>
<td>79.0</td>
<td>28.236</td>
<td>5 - 97</td>
<td></td>
</tr>
<tr>
<td>* MCMI-II Dysthymia (N=8)</td>
<td>88.3</td>
<td>5.574</td>
<td>77 - 97</td>
<td></td>
</tr>
<tr>
<td>MCMI-II Anxiety (N=8)</td>
<td>75.6</td>
<td>28.784</td>
<td>5 - 105</td>
<td></td>
</tr>
<tr>
<td>* MCMI-II Anxiety (N=8)</td>
<td>84.4</td>
<td>12.118</td>
<td>68 - 105</td>
<td></td>
</tr>
</tbody>
</table>

One subject did not complete the MCMI-II. ("**" indicates the removal of the outlier score.)

Subjects experienced significant chronic stress related to their MS. Many were anxious that either continued forgetfulness would result in their being fired, or not being promoted. Others mentioned continued financial and familial / marital difficulties. In addition, subjects described being "wiped out" by the "continual humiliation" and disability resulting from symptoms (e.g., incontinence).
Half the subjects experienced significant stressful events during this research: one subject, when at home, had "watched herself" raise a loaded gun to her head, feeling it was not herself; in one, a confirmation of pregnancy; there were two marital separations; one person's child diagnosed with Tourette's Syndrome; and one subject had a MS exacerbation. A few subjects attended the assessments, knowing their families / doctors disapproved. In one case, a family member was actively resistant to the research, claiming that "it was nonsense" and that any "quirks" had been there "before [onset of MS]". Conversely, other family members were delighted and felt their "instinct" that something was wrong, was confirmed.

Table 5
OTHER INDICES OF MENTAL STATUS: (N=10)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Subjects who have considered suicide in the past, or considered themselves seriously depressed:</td>
<td>10</td>
</tr>
<tr>
<td>Subjects who have in the past, received professional help for depression:</td>
<td>7</td>
</tr>
<tr>
<td>Subjects on anti-depressants or who feel depressed:</td>
<td>7</td>
</tr>
<tr>
<td>Subjects who currently describe themselves as depressed:</td>
<td>5</td>
</tr>
<tr>
<td>Subjects currently on anti-depressants or benzodiazepines:</td>
<td>5</td>
</tr>
<tr>
<td>Subjects with depression, suicide or alcoholism amongst immediate family members:</td>
<td>6</td>
</tr>
<tr>
<td>Subjects where an immediate family member has committed suicide (including grandparents and first cousins):</td>
<td>4</td>
</tr>
</tbody>
</table>
3.3. CLINICAL OBSERVATIONS

Many subjects found the assessment process stressful and felt they "had to impress" the examiner with their intelligence. In neuropsychological tests where difficulties were encountered, some subjects felt humiliated and ashamed. One subject wept when unable to perform at a level she had anticipated she should be able to. Despite constant reminders, three subjects forgot appointments. Throughout the clinical interviews, subjects commonly lost track of the conversation (e.g., "What was I going to say? What on earth was it?").

3.4. NEUROPSYCHOLOGICAL TEST RESULTS

Cognitive deficits were confirmed by neuropsychological test results. Performances varied noticeably between subjects.

3.4.1. Intelligence

The mean Full Scale Intelligence Quotient (FSIQ) was within the superior range. Four subjects scored in the superior range, four in the high average range, and one in the average range of general intelligence. On average, VIQ was nine points higher than PIQ. (See Table 6.) Subtest score means were lowest for Object Assembly, Digit Symbol and Arithmetic. However, mean subtest scores were never below the mean for the general population. Subjects performed best on Similarities, Picture Completion, Digit Repetition, Comprehension and Picture Arrangement.
Table 6 SAWAIS Results (N=9)

<table>
<thead>
<tr>
<th>SAWAIS TEST</th>
<th>MEAN</th>
<th>STD DEV</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSIQ</td>
<td>121.889</td>
<td>10.729</td>
<td>108.0 - 143.0</td>
</tr>
<tr>
<td>VIQ</td>
<td>126.222</td>
<td>10.485</td>
<td>116.0 - 148.0</td>
</tr>
<tr>
<td>PIQ</td>
<td>117.333</td>
<td>13.426</td>
<td>91.0 - 138.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAWAIS Subtests</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td>11.111</td>
<td>1.193</td>
<td>8.5 - 12.0</td>
</tr>
<tr>
<td>Comprehension</td>
<td>13.111</td>
<td>3.140</td>
<td>9.0 - 18.5</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>10.556</td>
<td>1.590</td>
<td>8.0 - 13.0</td>
</tr>
<tr>
<td>Digit Repetition</td>
<td>13.444</td>
<td>1.357</td>
<td>11.0 - 15.5</td>
</tr>
<tr>
<td>Similarities</td>
<td>15.111</td>
<td>1.516</td>
<td>13.0 - 18.0</td>
</tr>
<tr>
<td>Picture Completion</td>
<td>13.556</td>
<td>1.776</td>
<td>10.0 - 15.0</td>
</tr>
<tr>
<td>Object Assembly</td>
<td>10.333</td>
<td>2.000</td>
<td>7.0 - 14.0</td>
</tr>
<tr>
<td>Block Design</td>
<td>11.278</td>
<td>1.622</td>
<td>10.0 - 15.0</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>10.500</td>
<td>2.236</td>
<td>6.5 - 13.0</td>
</tr>
<tr>
<td>Picture Arrangement</td>
<td>13.111</td>
<td>1.816</td>
<td>10.5 - 15.5</td>
</tr>
</tbody>
</table>

3.4.3. Tests of Attention
The means for both TMT-A and TMT-B were below the 50th percentile. (See Table 7.) Eight subjects scored at or below the 30th percentile and the two other subjects scored at the 63rd and 78th percentiles, respectively. Of note, subjects performed better on TMT-B. Only four subjects performed below the 30th percentile, and
four scored above the 50th. The highest percentile score for TMT-B was at the 88th percentile. In contrast, performance on DF (SAWAIS) was superior and relatively consistent for all subjects. Subjects also performed above average on VMS (WMS-R), which was commensurate with their performance on Digits Forward (SAWAIS).

Table 7. Tests of Attention (N=10)

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Mean Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT-A (in seconds)</td>
<td>50.7</td>
<td>20.3</td>
<td>25 - 82</td>
<td>26th</td>
</tr>
<tr>
<td>TMT-B (in seconds)</td>
<td>98.8</td>
<td>53.3</td>
<td>46 - 219</td>
<td>41st</td>
</tr>
<tr>
<td>DF (SAWAIS)</td>
<td>7.889</td>
<td>0.78</td>
<td>7 - 9</td>
<td></td>
</tr>
<tr>
<td>VDF (VMS, WMS-R)</td>
<td>5.7</td>
<td>0.483</td>
<td>5 - 6</td>
<td>83rd</td>
</tr>
</tbody>
</table>

3.4.5. Tests of Learning and Memory

Prospective memory was impaired in most subjects (N=8). (See Table 8.) Four subjects failed to remember any tasks, and only two were able to recall all three. On the episodic memory questions, subjects tended to perform better, but often relied on customary routines to do so; "I always have a slice of toast for breakfast". Many complained of "going blank".

On tests of working memory, the mean performance on auditory tasks (i.e., Serial Sevens, DB (SAWAIS)) was superior to the mean of visual working memory tasks (VDB (WMS-R), TMT-B). On Serial
Sevens, all the subjects scored four or five out of five. The mean score on DB (SAWAIS) was 6.1, which was well above average. However, on VDB (WMS-R) the percentile performance dropped to the 68th percentile. As mentioned, on TMT-B, almost half the subjects scored below the 30th percentile.

Subjects performed poorly on the RAVLT, with subjects scoring a mean of 5.8 words for Trial 1. Eight subjects failed to score above the 50th percentile on any of the five trials. The other two subjects consistently scored at the 70th to 80th percentile range. All but one subject displayed a learning curve over the five trials on RAVLT, and on average had learned five extra words by their fifth trial. As expected, recognition memory was preserved, with almost all (N=8) correctly identifying 14 or 15 target words. There was minimal forgetting on delayed recall, with subjects forgetting, on average, only one word. There were few examples of confabulations and repetitions in the list learning.

On Logical Memory, the mean was below the 50th percentile. Nonetheless, compared to the RAVLT, subjects performed better on this task where the story's logic could aid memory recall. Only one subject scored below the 40th percentile, and almost half above the 50th percentile. On delayed recall, there was a slight drop in performance, with subjects, on average, forgetting one word or concept.
There was a wide range of performance for auditory new learning. Almost half the group learned the Digit Supraspan within two to three trials. One person was unable to learn the DSS despite ten attempts, although this subject was able to learn the VSS.

Three subjects were unable to learn the HBVR visuospatial pattern (N=9). However, as with RAVLT, subjects did well on recognition (as expected), and delayed memory tasks. All of the subjects scored the maximum on visual recognition (i.e., nine out of nine), and displayed minimal deterioration with delayed memory tasks. Two subjects were unable to learn a visual supraspan (N=10).

With complex visual memory (e.g., ROCF), scores were significantly below normal. Although the subjects demonstrated excellent visuographic copying skills on the ROCF, the mean percentile for ROCF memory was low at the 26th percentile.

On Digit Symbol Incidental Recall (SAWAIS), performance varied markedly. Subjects' recall ranged from two to nine symbols. The mean (six out of nine) was below the norm.

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective Memory:</td>
<td>1.4</td>
<td>1.265</td>
<td>0 - 3</td>
<td>3</td>
</tr>
<tr>
<td>Episodic Memory:</td>
<td>2.9</td>
<td>.876</td>
<td>1 - 4</td>
<td>4</td>
</tr>
</tbody>
</table>
### Tests of Working Memory (N=10)

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Mean Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial Sevens:</td>
<td>4.6</td>
<td>.5</td>
<td>4 - 5</td>
<td></td>
</tr>
<tr>
<td>Digits Backward:</td>
<td>6.111</td>
<td>0.928</td>
<td>4 - 7</td>
<td></td>
</tr>
<tr>
<td>VDB (WMS-R):</td>
<td>4.5</td>
<td>0.527</td>
<td>4 - 5</td>
<td>68th</td>
</tr>
<tr>
<td>TMT-B (in seconds):</td>
<td>98.8</td>
<td>53.3</td>
<td>46 - 219</td>
<td>41st</td>
</tr>
</tbody>
</table>

### Tests of Auditory Memory (N=10)

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Mean Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey Auditory Verbal Learning Task</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial 1:</td>
<td>5.8</td>
<td>2.530</td>
<td>1 - 9</td>
<td>34th</td>
</tr>
<tr>
<td>Trial 2:</td>
<td>8.0</td>
<td>2.449</td>
<td>4 - 13</td>
<td>33rd</td>
</tr>
<tr>
<td>Trial 3:</td>
<td>9.5</td>
<td>2.877</td>
<td>4 - 14</td>
<td>27th</td>
</tr>
<tr>
<td>Trial 4:</td>
<td>10.2</td>
<td>2.201</td>
<td>8 - 14</td>
<td>21st</td>
</tr>
<tr>
<td>Trial 5:</td>
<td>10.7</td>
<td>2.359</td>
<td>6 - 14</td>
<td>27th</td>
</tr>
<tr>
<td>List B:</td>
<td>5.9</td>
<td>1.197</td>
<td>4 - 8</td>
<td>31st</td>
</tr>
<tr>
<td>Recognition, +ve:</td>
<td>13.6</td>
<td>1.897</td>
<td>9 - 15</td>
<td></td>
</tr>
<tr>
<td>Recognition, -ve:</td>
<td>0.7</td>
<td>1.059</td>
<td>0 - 3</td>
<td></td>
</tr>
<tr>
<td>Trials 5 minus 1:</td>
<td>4.9</td>
<td>1.969</td>
<td>1 - 9</td>
<td></td>
</tr>
<tr>
<td>Repetitions:</td>
<td>2.7</td>
<td>3.529</td>
<td>0 - 11</td>
<td></td>
</tr>
<tr>
<td>Confabulations:</td>
<td>1.2</td>
<td>1.687</td>
<td>0 - 5</td>
<td></td>
</tr>
<tr>
<td>Delayed recall:</td>
<td>9.1</td>
<td>2.767</td>
<td>5 - 13</td>
<td></td>
</tr>
<tr>
<td>Logical Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate:</td>
<td>12.6</td>
<td>4.526</td>
<td>6 - 22</td>
<td>48th</td>
</tr>
<tr>
<td>Delayed:</td>
<td>11.7</td>
<td>4.373</td>
<td>5 - 20</td>
<td>45th</td>
</tr>
<tr>
<td>SAWAIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Supraspan:</td>
<td>4.556</td>
<td>2.297</td>
<td>2 - 9</td>
<td></td>
</tr>
</tbody>
</table>
Tests of Visual Memory

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Mean Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Digit Span (WMS-R) (N=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSS:</td>
<td>7.3</td>
<td>2.527</td>
<td>4 - 11</td>
<td></td>
</tr>
<tr>
<td>HBVR (N=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials to learn:</td>
<td>6.6</td>
<td>3.539</td>
<td>2 - 11</td>
<td></td>
</tr>
<tr>
<td>Total Errors:</td>
<td>11.6</td>
<td>15.241</td>
<td>0 - 45</td>
<td></td>
</tr>
<tr>
<td>Recognition:</td>
<td>9.0</td>
<td>0.000</td>
<td>9 - 9</td>
<td></td>
</tr>
<tr>
<td>Delayed:</td>
<td>7.8</td>
<td>1.093</td>
<td>6 - 9</td>
<td></td>
</tr>
<tr>
<td>ROCF (N=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copy:</td>
<td>35.2</td>
<td>1.229</td>
<td>33 - 36</td>
<td>90th</td>
</tr>
<tr>
<td>Memory:</td>
<td>17.5</td>
<td>4.620</td>
<td>12 - 25</td>
<td>26th</td>
</tr>
<tr>
<td>SAWAIS (N=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSIR:</td>
<td>6.0</td>
<td>2.345</td>
<td>2 - 9</td>
<td></td>
</tr>
</tbody>
</table>

3.4.4. Tests of Language

Despite adjustments for age, sex and years of education, the mean percentile performance (55th percentile) on COWAT was significantly less than expected, given the mean general intellectual performance of the subjects. (See Table 9.) As with the general population (Lezak, 1983), mean performance was better on the semantic cues over two categories, when compared to phonemic cues. All the subjects responded promptly and accurately on the Renfrew Word Naming Test.
Table 9. Tests of Language (N=10)

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Mean Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renfrew:</td>
<td>57.4</td>
<td>1.506</td>
<td>54 - 59</td>
<td></td>
</tr>
<tr>
<td>CFL / minute:</td>
<td>41.6</td>
<td>10.71</td>
<td>23 - 57</td>
<td>55th</td>
</tr>
<tr>
<td>Semantic:</td>
<td>17.3</td>
<td>5.539</td>
<td>8 - 25</td>
<td></td>
</tr>
</tbody>
</table>

3.4.6. Tests of Abstract / Reasoning Ability

On the WCST, eight subjects were able to predict sequences within three trials, while two failed to. (See Table 10.) More than half the subjects (N=6) were able to predict the first criterion within 13 attempts (the norm) (Heaton, 1981). However, the mean error score was elevated by the other subjects who struggled to predict the sorting category. By the second trial, three subjects were able to shift the set within five attempts, and by the last trial, eight were able to predict the new sequence within five attempts. However, the mean rose for the last trial, as the other two subjects were unable to predict the pattern, and scored the maximum of 50 errors. One subject became angry and accused the examiner of "unfairly" changing the pattern "every time". On Similarities (SAWAIS), subjects performed significantly above the mean for the general population.
### Table 10. Tests of Abstract / Reasoning Ability

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>WCST: (Number of errors) (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1:</td>
<td>15.1</td>
<td>15.308</td>
<td>3 - 50</td>
<td></td>
</tr>
<tr>
<td>Trial 2:</td>
<td>8.3</td>
<td>7.088</td>
<td>2 - 25</td>
<td></td>
</tr>
<tr>
<td>Trial 3:</td>
<td>12.1</td>
<td>19.991</td>
<td>2 - 50</td>
<td></td>
</tr>
<tr>
<td>SAWAIS (N=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities:</td>
<td>15.1</td>
<td>1.516</td>
<td>13 - 18</td>
<td></td>
</tr>
</tbody>
</table>

### 3.4.2. Tests of Handmotor Dexterity

Most of the subjects struggled on the GPT, and some were unable to feel or manipulate the grooved pegs. For each hand, every subject scored beneath the 50th percentile, and eight scored below the first percentile. (See Table 11.) No subject took more than five minutes to complete the board.

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
<th>Mean Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grooved Pegboard (in seconds)</td>
<td></td>
<td></td>
<td></td>
<td>Mean Percentile</td>
</tr>
<tr>
<td>Right Hand:</td>
<td>108.8</td>
<td>33.529</td>
<td>60 - 161</td>
<td>8th</td>
</tr>
<tr>
<td>Left Hand:</td>
<td>146.7</td>
<td>66.622</td>
<td>73 - 265</td>
<td>7th</td>
</tr>
</tbody>
</table>

### 3.5. MRI RESULTS

Of the ten subjects, eight underwent MRI investigations. (See Table 12.) One pregnant subject was excluded on the advice of the Chief Radiographer and another left the study before her MRI was done.
Table 12. MRI Results (in millimetres) \((N=8)\)

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Diameter</td>
<td>181.717</td>
<td>94.047</td>
<td>51.28 - 350.48</td>
</tr>
<tr>
<td>Right Diameter</td>
<td>97.984</td>
<td>44.529</td>
<td>35.90 - 156.19</td>
</tr>
<tr>
<td>Left Diameter</td>
<td>83.733</td>
<td>59.565</td>
<td>11.91 - 196.19</td>
</tr>
<tr>
<td>Total No. Lesions</td>
<td>35.125</td>
<td>16.505</td>
<td>7 - 57</td>
</tr>
<tr>
<td>Right No. Lesions</td>
<td>19.875</td>
<td>10.092</td>
<td>5 - 37</td>
</tr>
<tr>
<td>Left No. of LesNs</td>
<td>15.250</td>
<td>8.746</td>
<td>2 - 27</td>
</tr>
</tbody>
</table>

**Site of corpus callosal atrophy:**
- No atrophy: 4
- Anterior: 2
- Posterior: 1
- Whole of CC: 1

**Degree of callosal atrophy:**
- None: 4
- Mild: 3
- Severe: 1

**Ventricular dilatation:**
- None: 3
- Mild to moderate: 2
- Moderate: 1
- Moderate to severe: 1
- Severe: 1

**Brain Stem Lesions:**
- Yes: 2
- No: 6

Half the subjects who underwent MRI scans had minimal or no evidence of corpus callosal atrophy or ventricular dilatation. The number of lesions per subjects varied markedly (from seven to 57), and on average, there were more lesions visible in the right hemisphere.

Six subjects made earlier MRI scans available to the neuroradiologist. Although not specifically looked-for, the "waxing-waning" nature was evident, when compared to earlier MRI scans. For three subjects, there were decreases in the number of lesions and total summed diameter of plaques, or less atrophy apparent.
4.1. INTRODUCTION

Multiple sclerosis is a disease beset with problematic diagnoses, unpredictable prognoses, and "invisible" symptoms (Thornton & Lea, 1992). Most cognitive symptoms tend to be experienced subjectively, and are often not recognized by other people. Typically, psychological reactions may be to exacerbate or deny these symptoms (Harrower, 1987; McDonald & Silberberg, 1986).

This research was primarily concerned with the subjective experience of cognitive difficulties in people with MS. Subjects struggled to legitimize their experience of cognitive deficits to themselves and to others. With few exceptions, subjects experienced chronic stressful circumstances, both related and unrelated to their cognitive difficulties. On tests of mental state screening measures and general intelligence, there was no evidence of cognitive deterioration. However, on sophisticated neuropsychological testing, there was convincing evidence of cognitive problems, commensurate with a subcortical dementia. Lesions on MRI were not typical of the reported incidence of ventricular dilatation and corpus callosal atrophy in MS patients with cognitive deficits.
4.2. SUBJECTIVE EXPERIENCE: ANXIETY AND UNCERTAINTY

The most striking feature of this research was the pervasive and elevated levels of anxiety and insecurity experienced by the subjects. This anxiety was expressed in many ways, from "forgetting" appointments, to high scores on anxiety questionnaires, to breaking down during testing sessions, and the articulation of fears and self-doubt.

The debate between "is it real?" or "is it imagined?" was stressful as subjects struggled to come to terms with subtle cognitive symptoms. In some subjects, the fact that their cognitive symptoms would "come and go", heightened their lack of confidence. Often MS patients feel "frauds", and the need to know or confirm that what they experience is not imagined, can be compelling. This also contributed to feelings of inadequacy and dysthymia.

A neuropsychological assessment of this nature places enormous demands on the person being tested, and one cannot underestimate the stress involved for a person who may dread the outcome. When subjects "forgot" appointments, it was difficult to establish whether this was due to anxiety or forgetfulness. For the subjects, the choice was either "proof" of cognitive deterioration (and the fantasies of dementia), or evidence that they were "emotional" or neurotic, and "making it all up". Despite the fears of dementia, most preferred that their subjective experience of cognitive deficits would be validated by the assessment.
4.3. INTELLIGENCE AND EDUCATION

The second striking feature about this research, was the superior mean intelligence of the subjects. In all other studies known to this researcher, the FSIQ, VIQ and PIQ were reported as average (Izquierdo et al., 1991; C. G. Mathews et al., 1970; McIntosh-Michaelis et al., 1991; Rao et al., 1991a), while, in this group, the FSIQ and VIQ were superior, and the PIQ high average.

As the subjects were volunteers there were limits to the number of variables that could be controlled. The mean number of years of formal education was also higher than in other studies. Further, an age limit may also have had an influence on the high mean intelligence.

It is possible that people who invest in their intelligence as a primary important self-identity are more likely to be threatened by, and be conscious of, cognitive changes. A resultant "hypersensitivity" to cognitive changes, experienced or imagined, may thus occur more readily in subjects with superior intellectual functioning. People with higher investment in their intelligence may be more likely to fear cognitive deterioration. Further, people who are more worried about the occurrence of cognitive deterioration, may be more willing to volunteer for related research.
4.4. RESULTS: NEUROPSYCHOLOGICAL TESTS

In such highly educated and younger subjects, scores in the "average" range, represent decline in cognitive performance. Mean percentile scores below the 89th percentile (the mean intellectual functioning performance) must thus be explained.

Despite the differences in the mean intellectual performances, distributions on the SAWAIS concurred with other research. On average, PIQ is 7-14 points less than VIQ, Digit Symbol is the lowest, and Picture Completion the highest PIQ score (Rao, 1986). This study replicated these findings, and confirmed that the subjects experienced neuropsychological deficits.

Many MS patients have impaired sensory (e.g., numbness, proprioceptive loss) and fine motor functioning. Thus, people with MS tend to perform poorly on tests of motor dexterity and tests sensitive to deficits in speed and capacity of processing (Grigsby et al., 1994), such as the GPT, TMT and Digit Symbol (SAWAIS). On the GPT and TMT, subjects' mean performance was significantly slower when compared with MS patients in Klonoff et al. (1991). However, performance was superior, when compared to C. G. Mathews et al. (1970).

There was some evidence of lateralization of function on tasks of attention {DF (SAWAIS) and VDF (WMS-R)}, and working memory {DB (SAWAIS) and VDB (WMS-R)}. Subjects' mean performance was two
digits longer on the auditory tasks, when compared to the visual equivalents. In addition, subjects performed poorly on the ROCF, a complex visual memory task. Together, these raise the possibility of right hemisphere involvement. However, further examination of the auditory memory test profile suggested contralateral pathology.

There were substantial impairments evident in both prospective and episodic memory. Many subjects appreciated these impairments to be "exactly what happens all the time!", contributing to situations of embarrassment and humiliation. Some subjects expressed relief to be able to confirm for themselves, that they had these difficulties, and that their memory problems were identifiable by a name (e.g., "prospective memory").

On multitrial learning tasks, the average performance of MS patients is usually impaired on the first trial, implying some aspect of encoding is impaired. Thereafter, learning proceeds at a normal rate, and the proportion of material retained after a delay within normal limits (Minden et al., 1990b; Beatty, 1993). Again, on the RAVLT and HBVR, this research replicated these findings, including relatively preserved delayed memory and recognition skills.

Normally, Digits Forward (DR, SAWAIS) and the number of words recalled on RAVLT Trial I should be within one or two points of each other (Lezak, 1983). However, patients with intact immediate
memory who become confused by too much stimulation tend to show larger differences (favouring DF). Lezak (1983) found such patients to have difficulty with complex material (or situations of any kind), but found them to do better on simplified, highly structured tasks. The poorer relative performance of RVALT Trial I recall when compared to the DF (DR, SAWAIS), was probably in due to information overload.

Compared to RAVLT, there were relatively better accomplishments on passage recall (Logical Memory), although performance was still impaired. Possibly, the story's logic acted as a cue, assisting subjects' memory.

On tasks of verbal fluency, MS patients are consistently impaired (Beatty, 1993). Although the mean percentile for the subjects was above the 50th percentile, it was lower than expected for people with their obvious intellectual potential.

Abstract thinking is frequently reported as impaired in the MS literature on cognition (Rao, 1993). However, in this study, performance on Similiarities (SAWAIS) and WCST, a test of executive function, was intact.

4.5. THE MRI
Half of the people undergoing MRI investigations had no corpus callosal (CC) atrophy, and no or minimal ventricular dilatation.
The mean accumulative diameter across all the plaques was less than 20cm. This is atypical of many MRI studies examining MS and cognition, where CC atrophy, ventricular dilatation, and a total plaque diameter in excess of 20 to 30cm is usually described in patients suffering cognitive deficits.

While postmortem studies have shown MS lesions to be distributed evenly across both hemispheres (Rao, Hammcke, McQuillen, Khatri & Lloyd, 1984), this research evidenced a greater mean total number of lesions (TNL) in the right hemisphere. This may be explained by a the small sample size, and thus Type II error. Nonetheless, the greater number of lesions in the right hemisphere found in this research is of interest, given the lateralized results in attention and working memory tasks.

The clinical significance of such lesions however, remains controversial (Comi et al., 1993; Smith et al., 1993). Even if patients have virtually identical MRI results, a marked variability in cognitive test performance may occur (Feinstein, Ron & Thompson, 1993). Silent lesions (lesions without corresponding symptoms) (Warren, Warren & Cockerill, 1991) are common on MRI, and new lesions can occur at approximately ten times the frequency of new clinical episodes (Rao, 1990). In addition, detectable abnormalities could represent lesions in different stages of evolution (Ron et al., 1991).
Multiple sclerosis lesions are not static. Some subjects had few lesions at the time of testing, compared to previous MRI scans. It would be necessary to match the waxing / waning nature of the number and position of the lesions, against performance on neuropsychological testing, in order that the effect of lesions can be clearly defined. The waxing and waning nature of the lesions imply that cognitive deficits in MS may fluctuate. This possibility is supported by the subjects' accounts of their personal experiences.

4.6. THE NEED TO ACKNOWLEDGE

While cognitive impairment in MS patients as a fact of illness is accepted within the neuropsychological community, this cannot be said of the neurological community at large (Rao, 1990). Despite the fact that for over a century it has been recognized that affective and cognitive symptoms are prevalent in multiple sclerosis, cognitive symptoms in MS have been largely ignored or denied. Subjects who did suffer from memory and concentration difficulties were often told it was due to other problems, mostly "stress", and that it was not caused by MS. This can lead to feelings of distrust - with MS patients feeling that medical professionals are withholding information (Thornton & Lea, 1992), and with professionals fearing that they have to treat "yet another hysterical" patient. This is not to deny that at times, a patient may present with a pseudodementia.
Part of the reason for the lack of acknowledgment, is that many neurologists themselves are ignorant of the possible cognitive consequences brought about by MS. Further, with contradictions and overestimations of cognitive deficits being frequently published, medical practitioners may be skeptical of the literature. A balance between unnecessary alarm and realistic response must be reached (Rao, 1990).

Of all a human's faculties, probably intellectual capacity is the most valued (Rao, 1990). Together with sexual dysfunction difficulties, many medical practitioners are uncomfortable in imparting such potentially devastating news (Ron & Feinstein, 1992) - especially when the aetiology of the symptoms remains so unclear. In addition, unlike physical symptoms, cognitive impairment does not respond to short courses of corticosteroids (Rao et al., 1993), leaving the medical practitioner helpless to assist the patient.

It has been shown that clinical neurologists will miss significant cognitive dysfunction in up to half the patients they examine (Beatty & Goodkin, 1990b). Mild cognitive impairment can easily go undetected. Cognitive deficits, even for neurologists sensitive to the issues, are often difficult to recognize in patients with MS (Rao et al., 1993). Brief standardized mental status examinations (e.g., the MMSE) and standard clinical neurological examinations may be insensitive even to moderate cognitive impairment (Peyser et al., 1990; Prosiegel & Michael, 1993). From this research, it is
evident that even MS patients with minimal or no corpus callosal atrophy, no ventricular dilatation, relatively few lesions and a low accumulative plaque diameter, still have cognitive deficits.

Even if neurologists who treat MS patients suspect cognitive deficits, they may hesitate to refer the patient for additional neuropsychological testing, given the considerable cost and time required for a truly thorough examination of cognitive capacity. As a simple rule of thumb, Beatty and Goodkin (1990b) recommend that any MS patient (especially those with a high school education, and without severe disability) who score below the norm on the MMSE, require additional neuropsychological evaluation.

It is important that cognitive difficulties be recognized as common symptoms in MS, as recognition can lead to acknowledgement and treatment. Confirmation (of a chronic illness or a symptom within it) can lead to relief and comfort. It legitimizes the person's experiences and needs. Understanding what is happening minimizes the stress related to "not knowing", and can empower the patient with knowledge and acceptance. This not only occurs with the initial diagnosis of physical symptoms (which for many patients follows a traumatic period of not only "not knowing", and not being believed), but also with the experience of cognitive deficits. Often it is possible that the person can learn to compensate for their impairments.
4.7. COGNITIVE RETRAINING AND PSYCHOSOCIAL INTERVENTION

While there has been extensive research into the cognitive functioning of people with MS, as yet there has been minimal research into cognitive retraining. However, the field of neuropsychology is currently shifting from mere diagnosis per se towards more description, explanation and rehabilitation (R. Taylor, 1990).

Many patients with MS have a benign course and are suitable for long-term neuropsychological treatment (Prosiegel & Michael, 1993). Remediation (partial or complete restoration of impaired function via therapy, e.g., speech therapy), adaption (with external aids), and compensation and accommodation (via residual or undisturbed functions) are all imperative. Restorative techniques, targeted at specific cognitive tasks, (Rao et al., 1993) have enjoyed particular success. Recently, computer-assisted memory remediation programmes and pharmacological manipulation (Peyser et al., 1990) have been applied in cognitive retraining programmes.

More simply, keeping diaries, displaying large month-planners, and cautioning family members to remind, are effective ways of dealing with the more mild and commonly experienced memory difficulties. Not surprisingly, all the people in this research had instinctively turned to some form of self-help compensation.

Because of the heterogeneity of the illness, programmes need to
consider individual needs. Despite the differing psychosocial experiences, MS patients experiencing cognitive symptoms are all eligible recipients for a counselling programme which deals with grief work, self-image, and anxiety management. Even if the patient mistakenly believes they suffer such cognitive deficits, then a programme of counselling around these issues remains necessary. It may be that in cases of pseudodementia, the underlying causes can be remedied and the cognitive deficits reversed.

This research demonstrates the fundamental importance of assessing anxiety and depression in MS patients presenting with cognitive symptoms. Therefore, any efforts at cognitive retraining and psychosocial intervention should as a matter of course, include stress management and examination of the factors causing the anxiety. Counselling targeted at improving self-image and recognizing the symbolic and functional importance of cognitive abilities can relieve much of the associated stress.

4.8. ESTABLISHING AN AETIOLOGY

Neuropsychiatric dysfunction in people who have multiple sclerosis can be independent of, and merely coincidental to MS; or predominantly reactive to the stresses inherent in the illness; or directly related to the lesions of the disease (Honer et al., 1987). In addition, when MS patients are on medication, the
pharmacological influences on test performance must be accounted for. In this study, a pharmacologist carefully assessed the influences of each subject's medication on neuropsychological test performance. It is considered the sample is "relatively uncontaminated by medicines" (Dr A. Robbins, personal communication, March 8, 1995).

This research highlights the difficulty of unravelling the aetiological factors of cognitive dysfunction, with more than half the sample having familial and individual psychiatric histories, almost half the sample having an unrelated (to MS) cerebral assault (e.g., pulmonary embolism), and many experiencing significant stressful life events (e.g., two marital separations). One subject had a relapse, where typically the subjective response to a deterioration in physical well-being can lead to considerable stress and depression (Feinstein et al., 1993). And in turn, the above factors may influence psychometric test results. It is imperative that a thorough familial and individual history be conducted, and psychological well-being be assessed, in any research into cognitive functioning in MS.

Ron et al. (1991, p. 66) who, on interview, found 25/58 of the MS subjects to be psychiatric "cases", concluded that psychiatric symptoms and the cognitive deficits represented two "intricately linked" parameters. It is easy to appreciate the difficulty of isolating confounding variables and the extremely complex
relationship between them. The interaction of the organic, pharmacological, psychological, psychiatric and social factors are crucial to developing a model to explain the pathogenesis of cognitive and psychological changes in MS. It is only a multifactorial aetiology, that can make better sense and explain cognitive dysfunction in multiple sclerosis.

A plaintive cry, ending most researchers' conclusions on cognitive research in MS, is the call for longitudinal studies. It was the intention from the outset of this research, that the ten subjects be involved in a five-yearly follow-up. In this way, causal inferences (of necessity, limited in cross-sectional studies) can be made, and a clearer understanding of the interplay between cognitive and psychological paradigms, be obtained.

4.9. CONCLUSION

Psychiatric and cognitive symptoms can occur both in the early and in a later stage of the disease, and they cause much despair. Research (Ron & Feinstein, 1992) has shown that cognitively impaired MS patients experience more significant difficulties in work, social contact, sex and activities of daily living, than those without. In addition, MS patients with cognitive disability are less likely to receive disability benefits (or receive them later) than their physically disabled counterparts (Rao et al., 1991b).
Difficulties in memory, concentration, self-control and emotional expression can lead to feelings of guilt, misunderstanding, anger and rejection. Failure to recognize cognitive impairment can lead to unrealistic expectations and difficulties in family members' adjusting to a patient's disease. Without accurate information, relatives of cognitively impaired MS patients tend to attribute their problems to elective obstinacy, depression, or other forms of disturbance (Rao et al., 1991b). Lack of understanding may aggravate the stressful situation for the patient and the family.

"Feeling of knowing" (Beatty & Monson, 1991), is a term used to assess to what degree research participants can predict their own performance. It shows that subjective cognitive impairment reflected on neuropsychological testing is often related to functional impairment. More than that, the patient is "being taken seriously", and an acknowledgement that cognitive deficits may be "unseen", but nonetheless lead to disability. Therapy allows the patient and family to recognize and accept cognitive loss, and bestows understanding of the deteriorative nature of the disease.

All psychological and cognitive symptoms, whether organic or "emotional", need to be taken seriously, with regular referrals for neuropsychological assessment. Acknowledgement is a first, but vital step in ensuring fulfilled and dignified lives for people suffering from cognitive deficits.
4.10. LIMITATIONS AND SUGGESTIONS FOR FUTURE RESEARCH

4.10.1. Sample Size

A thorough neuropsychological examination may take two to six hours. While such lengthy testing is necessary for a comprehensive understanding a person's cognitive status, it becomes impractical for screening a large sample (Peyser et al., 1990). Time and resources meant that only ten people were included in the study, creating statistical limitations to the generalization of findings. While in a disease as heterogeneous as MS, it is important also to rely on in-depth, qualitative assessments, it is equally important to generate quantitative data on a larger sample.

4.10.2. MCMI-II

In this research, what was apparent, was the consistent and generalized psychological distress and disturbance amongst almost the entire sample in this study, with the means for both the MCMI-II anxiety and dysthymia scales elevated above the "clinical cutoff" point. However, it is important to remember that in interpreting these score results, that there is a tendency towards overpathologization.

Understandably, people with MS tend to be more acutely sensitive to bodily changes and more preoccupied with bodily functioning. Much of the criteria for anxiety and depression are based on somatic symptoms, allowing for significantly greater frequency of response in a "pathological" direction in an MS population. Some
researchers (Minden & Schiffer, 1993) thus suggest that such variables (fatigue, slowed thinking and poor concentration) should be excluded from the diagnostic criteria of depression in people with multiple sclerosis.

4.10.3. Relapsing Remitting versus Chronic Progressive

People with both RR and CP MS were included, despite the considerable evidence that cognitive dysfunction is particularly associated with a CP disease course. However, it is often unclear whether patients present a CP or RR course (Anzola et al., 1990). Longitudinal adherence to a disease type in MS is highly variable (Jennekens-Schinkel et al., 1990a), meaning that correlation with disease type and other disease-related variable may be expected to vary as time passes. A month after the study, one of the subjects phoned the researcher to say that her neurologist had re-classified her as having a CP course, and that she had "probably had it for ages!".

4.10.4. Future Research

Ideally, variables such as type of MS, whether or not in an active exacerbation, physical disability, disease duration, education, other cerebral trauma, medication, substance abuse, fatigue, pain and practice effects would be controlled. This study shows the necessity of a multifactorial aetiological model. In larger studies, multiple regression analysis could control these factors
individually, leading to causative associations between the variables.
REFERENCES


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APPENDIX 1

ABBREVIATIONS
LIST OF ABBREVIATIONS

In the Text:

APA American Psychiatric Association
CNS Central Nervous System
CP Chronic Progressive (course of multiple sclerosis)
MDE Major Depressive Episode
MRI Magnetic Resonance Imaging
MS Multiple Sclerosis
RR Relapsing Remitting (course of multiple sclerosis)

MRI-related abbreviations:

CC Corpus Callosum
PD Proton Density
LLA Left (hemisphere) Lesion Area (of all plaques)
LNL Left Number of Lesions
LPD Left Plaque Diameter
RLA Right (hemisphere) Lesion Area
RNL Right Number of Lesions
RPD Right Plaque Diameter
SE Spin Echo
TLA Total (left and right hemispheres together) Lesion Area
TNL Total Number of Lesions
TPD Total Plaque Diameter (summed diameter of all plaques)

Questionnaires and Tests:

BDI Beck Depression Inventory
BRS Base Rate Score
COWAT Controlled Oral Word Association Test
DB Digits Backward
DD Digits Difference
DF Digits Forward
DR Digit Repetition
DSIR Digit Symbol Incidental Recall
DSS Digit Supraspan
FSIQ Full Scale Intelligence Quotient
GHQ General Health Questionnaire
GPT Grooved Pegboard Test
HBVR Hopkins Board of Visual Recall
HRS Hamilton Rating Scale for Depression
IQ Intelligence Quotient
LM Logical Memory
MCMI Millon Clinical Multiaxial Inventory
MMSE Mini Mental State Examination
Questionnaires and Tests (continued):

- PIQ: Performance Intelligence Quotient
- RAVLT: Rey Auditory Verbal Learning Task
- RFIT: Rey Fifteen Item Test
- ROCF: Rey-Osterrieth Complex Figure
- RWFVS: Renfrew Word Finding Vocabulary Scale
- SAWAIS: South African Wechsler Adult Intelligence Scale
- SS: Supraspan
- TMT: Trail Making Test
- VDB: Visual Digits Backward
- VDF: Visual Digits Forward
- VIQ: Verbal Intelligence Quotient
- VMS: Visual Memory Span
- VSS: Visual Supraspan
- WCST: Wisconsin Card Sorting Task
- WMS-R: Wechsler Memory Scale - Revised

\[ \bar{x} \] Mean
\[ \text{SD} \] Standard Deviation
\[ \text{N} \] Number of participants in a sample

Places, Organizations and Institutions:

- CSD: Centre for Science Development
- GSH: Groote Schuur Hospital
- MRC: Medical Research Council of South Africa
- RSA: Republic of South Africa
- SANMSS: South African National Multiple Sclerosis Society
APPENDIX 11

THE

NEUROPSYCHIATRIC

INTERVIEW
NEUROPSYCHIATRIC INTERVIEW:

1) NAME (TITLE):
2) DOB:
3) AGE:
4) GENDER:
5) OCCUPATION:
6) YEARS OF EDUCATION:
7) HIGHEST EDUCATION:
8) MARITAL STATUS:
9) CHILDREN:
10) LIVES WITH:
11) ADDRESS:
12) TELEPHONE NUMBER:
13) HOME LANGUAGE:

14) DO YOU HAVE MS?
15) CHRONIC? ACUTE? OTHER? DON'T KNOW?
16) WHEN WERE YOU DIAGNOSED?
17) FROM WHEN CAN YOU REMEMBER YOUR FIRST MS SYMPTOMS?
18) WHAT ARE YOUR CURRENT COMPLAINTS?

19) WHAT DOES THE WORD "COGNITIVE" MEAN?
20) WHAT ARE YOUR COGNITIVE COMPLAINTS?
21) HISTORY OF COGNITIVE COMPLAINTS? (CHRONIC? COMES/GOES?)
22) CURRENT MOOD?
23) AFFECTIVE HISTORY?
24) CONTEXT OF COGNITIVE COMPLAINTS?
25) WHAT MAKES COGNITION WORSE? BETTER?
26) EFFECTS OF COGNITIVE PROBLEMS:
   (a) ON SELF ESTEEM
   (b) ON FAMILY
   (c) ON WORK
   (d) ON ATTITUDE TOWARDS THE FUTURE

27) WHAT DO YOU DO TO HELP YOURSELF COGNITIVELY?
28) WHAT MAKES YOU THINK YOUR COGNITIVE PROBLEMS ARE CAUSED BY THE MS?
29) WHEN DID YOU FIRST FIND OUT THAT MS COULD COGNITIVE PROBLEMS? WERE YOU TOLD TO EXPECT THEM?
30) HOW DID THIS MAKE YOU FEEL?
31) HOW DOES PARTICIPATION IN RESEARCH MAKE YOU FEEL?
32) WHAT DO YOU EXPECT YOUR RESULTS MAY INDICATE?
33) DO OTHERS ALSO FEEL YOUR COGNITIVE PROBLEMS ARE DUE TO THE MS?
34) WHAT ELSE MAY BE CONTRIBUTING TO YOUR COGNITIVE PROBLEMS?

35) FAMILY MEDICAL AND PSYCHIATRIC HISTORY:
36) HEAD INJURIES? LOC? PT'S MHx? PSYCHIATRIC Hx?
37) MEDICATION? PSYCHOTHERAPY?
38) SCHOOL HISTORY?
39) OCCUPATIONAL HISTORY?
40) BASIC PERSONALITY?
41) LEVEL OF FUNCTIONING?
42) DEPRESSION INVENTORY AND MSE