Memory Function In Multiple Sclerosis

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ABSTRACT

Multiple Sclerosis (MS) is a disease of the central nervous system. Its diffuse pathology results in a variety of physical and psychological symptoms. Memory dysfunction is one of the most prevalent cognitive deficits associated with MS. However, the accurate assessment of memory in MS is often compromised by the coincident physical and/or cognitive difficulties of the patients. Also, there are no conventional memory tests suitable for MS patients, which grade varying types of verbal and spatial memory ability. The aim of this thesis was to develop a new test of memory which reduced the handicap imposed by sensori-motor dysfunction on cognitive test performance, and assessed recall memory, paired association, and recognition memory using matched verbal and spatial tasks.

The New Test Of Memory was standardised using a sample of 85 healthy controls, stratified for age, sex, and IQ. The measure demonstrated the effects of ageing on normal memory performance, and showed good internal reliability (Cronbach's alpha verbal sections: 0.76; spatial sections: 0.75), consistency, and construct and factorial validity. The validation sample comprised 100 MS patients. The applicability of the tasks for patients with MS was demonstrated by the absence of a relationship between memory performance and measures of visual integrity and manual dexterity. The patient assessments also showed good internal reliability (Cronbach's alpha verbal sections: 0.85; spatial sections: 0.74), consistency, and construct, factorial, convergent, and discriminant validity. Patient performance was significantly impaired relative to controls, with 23 % of patients scoring more than 2 standard deviations below the age group control mean on the verbal sections, and 15 % on the spatial sections. The patterns of impairment demonstrated by the patients did not provide support for either the acquisition or retrieval deficit hypotheses, suggesting that memory deficiencies in MS may not fit a simple, single deficit model.

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CHAPTER ONE: INTRODUCTION

Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system, affecting the brain and spinal cord. It is one of the most common non-traumatic neurological conditions to affect young and middle-aged adults (Weinshenker, 1994). The exact cause of MS is as yet unknown, although the characteristic lesions, principally in the white matter (Brownell & Hughes, 1962), result from an immunologically mediated inflammatory response to a combination of environmental and genetic factors. Destruction of the myelin sheath around axonal fibres reduces the conduction ability of the neurones, leading to a wide variety of neurological symptoms. The white matter tracts most frequently affected are the optic nerve, corticospinal tract, cerebellar outflow systems and medial longitudinal fasciculus (McAlpine et al., 1955).

Different patterns of disease activity in MS have been described. Relapsing-remitting (RR) MS involves episodes of disease activity followed by periods of remission. Recovery from episodes may be partial or complete, and the periods between relapses are characterised by a lack of disease progression (Lublin & Reingold, 1996). RR MS typically evolves into secondary progressive (SP) MS, the classification which refers to the progressive course, with or without superimposed relapses, which succeeds the initial RR phase (Lublin & Reingold, 1996). Benign MS is thought to be a temporal variant of RR/SP MS in which there is little or no disability, and the patient remains fully functional in all neurological systems after 15 years (Lublin & Reingold, 1996). Primary progressive (PP) MS involves deterioration from the outset, with no history of relapses or remissions (Lublin & Reingold, 1996). Transitional progressive (TP) MS has

a predominantly progressive course, with only a single relapse either several years before the onset, just prior to it, or on one occasion during the progressive phase (Stevenson et al., 1999). Studies during the 1980s and early 1990s classified their MS patients using the simplified categorisation of RR or chronic-progressive (CP) disease types. However, the CP category has recently been shown to lack specificity (Lublin & Reingold, 1996), typically including patients with either PP or SP MS. PP and SP patients have been reported to demonstrate distinct MRI characteristics (Thompson et al., 1991), pathological differences (Revesz et al., 1994), and distinctive clinical courses (Thompson et al., 1997). Hence a group of MS patients classified as CP, will almost inevitably constitute a heterogeneous sample.

The different clinical forms of MS may be produced by distinct pathogenetic mechanisms (Lucchinetti et al., 1996). However, at present the evidence in favour of heterogeneity in the pathogenesis of MS is inconclusive (McDonald & Thompson, 1997). Alternatively, PP and TP MS may be thought of as featuring at one end of a broad spectrum of disease activity (McDonald & Thompson, 1997). RR MS may be considered to lie at the opposite end of the continuum to the PP form, with SP MS patients occupying an intermediate position between the two groups (Thompson et al., 1997).

1.1 COGNITIVE IMPAIRMENT: OVERVIEW

1.1.1 Incidence Of Cognitive Dysfunction:

Cognitive impairment as a feature of MS was first noted by Charcot (1877) who commented on patients' "enfeeblement of the memory" with "conceptions that formed slowly". However, several early researchers disputed this finding, recording cognitive dysfunction as a comparatively rare outcome of the disease, occurring in the late stages and often associated with severe physical disability (Cotterell & Wilson, 1926; Diers & Brown, 1950; Kurtzke et al., 1972). Studies which reported a very low incidence of cognitive impairment in MS patients typically did not employ formal neuropsychological tests, simply using brief neurological examinations (Peyser et al., 1990). They recorded the frequency of cognitive dysfunction in MS to be between 2% and 13% (Kurtzke et al., 1972; Peyser et al., 1980). With hindsight, the use of the Mini Mental State Examination (MMSE; Folstein et al., 1975) in the cognitive assessment of MS patients, provides an illustration of the inadequacies of brief screening measures as assessment tools for documenting the incidence of cognitive dysfunction. The MMSE was designed as a bedside cognitive screening instrument which takes five to 10 minutes to administer, and examines orientation for time and place, immediate recall, short-term memory, attention and calculation, constructional ability, and language. It has a maximum score of 30, and cognition is considered impaired if the individual attains a score below 24 (DePaulo & Folstein, 1978). Despite its brevity and ease of administration, the MMSE has been criticised for large false positive and false negative error rates (Nelson et al., 1986), and, furthermore, it has been shown to be insensitive to cognitive impairment in MS patients (Franklin et al., 1988; Beatty & Goodkin, 1990; Swirsky-Sacchetti et al., 1992a; Kujala et al., 1996a). Franklin et al. (1988) reported

60% of their patient group as impaired when using a comprehensive neuropsychological battery, none of which would have been identified using the standard cut-off of the MMSE (DePaulo & Folstein, 1978). Likewise, Beatty and Goodkin (1990), Swirsky-Sacchetti et al. (1992a), and Kujala et al. (1996a) noted that patients who exhibited significant cognitive dysfunction on neuropsychological tests often went undetected using the MMSE. These studies emphasise the importance of comprehensive neuropsychological assessment when determining the incidence of cognitive dysfunction in patients with MS.

In contrast to the research reporting intact cognition in MS, early studies which demonstrated cognitive deficiencies in such patients included Canter (1951), Ross and Reitan (1955), Jambor (1969), Beatty and Gange (1977), and Staples and Lincoln (1979). Jambor (1969) and Staples and Lincoln (1979) compared MS patients with individuals suffering from muscular dystrophy, and suggested that cognitive impairment in MS was not simply due to the presence of a chronic incapacitating disease, but resulted from the demyelination of the brain cerebral cortex.

Cognitive dysfunction in MS is now considered to be a relatively common occurrence (Heaton et al., 1985). Neuropsychological research suggests that up to 65% of MS patients will demonstrate some form of cognitive impairment (Parsons et al., 1957; Surridge, 1969; Staples & Lincoln, 1979; Rao et al., 1984; Heaton et al., 1985; Lyon-Caen et al., 1986; McIntosh-Michaelis et al., 1991; Rao et al., 1991). The frequency of such dysfunction reported in the literature fluctuates because of the heterogeneity of the neuropsychological assessments used and the varying criteria applied to categorise individuals as cognitively impaired. Studies may also examine different patient groups, with diverse demographic and clinical characteristics; MS patients recruited from research centres tend to have greater physical disability, and/or

more active disease than those in the community (Nelson et al., 1988). In one of the most representative studies to date, Rao et al. (1991a) administered a comprehensive neuropsychological battery to 100 community based MS patients and 100 demographically matched, healthy controls. 43% of the MS patients were categorised as cognitively impaired relative to the control group.

1.1.2 Cognitive Dysfunction And Clinical Variables:

Cognitive impairment in MS cannot be predicted precisely from any other aspect of the disease. There is little or no significant relationship between cognitive impairment and physical disability (Marsh 1980; Peyser et al., 1980; Rao et al., 1984; 1985; Lyon-Caen et al., 1986; Van den Burg et al., 1987; Beatty et al., 1988; Franklin et al., 1988; 1989; Rao et al., 1989a; 1989b; Jennekens-Schinkel et al., 1990a; Minden et al., 1990; Mariani et al., 1991; Ron et al., 1991; Maurelli et al., 1992; Patti et al., 1995), although some studies noted a correlation (Canter, 1951; Fink & Houser, 1966; Surridge 1969; Kurtzke 1970; Beatty & Gange, 1977; Staples & Lincoln, 1979; Huber et al., 1987; Beatty et al., 1989; Beatty et al., 1990a; McIntosh-Michaelis et al., 1991; Rao et al., 1991; Kessler et al., 1992; Basso et al., 1996; Troyer et al., 1996). The data regarding the relationship between cognitive function and disease duration are equally mixed, with a number of researchers reporting no correlation (Ivnik 1978a; Rao et al., 1984; 1985; Lyon-Caen et al., 1986; Beatty et al., 1988; Rao et al., 1989a; 1989b; Franklin et al., 1989; Beatty et al.,1990a; Jennekens-Schinkel et al., 1990a; Minden et al., 1990; Rao et al., 1991; Maurelli et al., 1992; Patti et al., 1995), and others noting a significant relationship (Grant et al., 1984; Heaton et al., 1985; Beatty et al., 1989; Callanan et al., 1989; McIntosh-Michaelis et al., 1990; Ron et al., 1991).

1.1.3 Cognitive Dysfunction And Depression:

Charcot (1877) and Baldwin (1952) provided early evidence that depression was associated with MS, and it has recently been shown that the lifetime risk of major depression in MS patients is approximately 50% (Sadovnik et al., 1996). However, depression has not been shown to have an adverse effect on cognitive performance. Although MS patients have been shown to be more depressed than healthy controls, or patients with other chronic neurological conditions (Whitlock & Siskind, 1980; Schiffer et al., 1986; Joffe et al.,1987; Minden & Schiffer, 1990), few studies have reported a correlation between depression scores and cognitive impairment (Surridge, 1969; Peyser et al., 1980; Lyon-Caen et al. 1986; Beatty et al., 1989; Rao et al., 1989b; Minden et al., 1990; Grafman et al., 1991; Rao et al., 1991; Schiffer & Caine, 1991; Krupp et al., 1994). Despite these findings, Filippi et al. (1994) recently linked frontal lobe dysfunction with depression.

1.1.4 Cognitive Dysfunction And Magnetic Resonance Imaging:

More robust predictors of cognitive impairment in MS come from magnetic resonance imaging (MRI), where poor cognitive performance has been correlated with total lesion load (Medaer et al., 1987; Brainin et al., 1988; Franklin et al., 1988; Callanan et al., 1989; Rao et al., 1989a; Anzola et al., 1990; Pozzilli et al., 1991a; Ron et al., 1991; Feinstein et al., 1992a; Huber et al., 1992; Maurelli et al., 1992; Pozzilli et al., 1992; Swirsky-Sachetti et al., 1992b; Comi et al., 1993; Pugnetti et al., 1993; Comi et al., 1995; Patti et al., 1995; Hohol et al., 1997; Rovaris et al., 1998, Camp et al., 1999), atrophy of the corpus callosum (Huber et al., 1987; Rao et al., 1989a; Pozzilli et al., 1991b; Huber et al., 1992; Pozzilli et al., 1992; Swirsky-Sachetti et al., 1992b; Comi

et al., 1993), ventricular dilation (Pozzilli et al., 1991a; Clark et al., 1992; Swirsky-Sachetti et al., 1992b; Comi et al., 1993), magnetisation transfer ratio (Rovaris et al., 1998; Van Buchem et al., 1998), and a measure of cerebral atrophy (Camp et al., 1999). Recently, some studies have attempted to relate the location of cerebral white matter lesions in MS patients to specific patterns of cognitive test performance (Arnett et al., 1994; Swirsky-Sacchetti et al., 1992b). However, Foong et al. (1997) disputed the suggestion of finding a relationship between specific cognitive deficits and focal brain lesions in MS, which is a disease with such a diffuse pathology.

1.1.5 Summary:

- MS is a chronic demyelinating disease of the central nervous system, which can be divided into several specific subtypes. It is unclear whether these forms feature at differing points within a spectrum or continuum of disease activity, or are distinct disease entities (Introduction).
- Recent studies using comprehensive neuropsychological assessments have suggested that cognitive dysfunction may be exhibited by as many as 65% of MS patients (Section 1.1.1).
- Cognitive impairment cannot be predicted precisely from clinical characteristics, such as disease duration or physical disability (Section 1.1.2).
- Although depression is associated with MS, there is little evidence to suggest that it has a significant impact on cognitive impairment (Section 1.1.3).
- Various MRI parameters have been reported to provide relatively robust predictors of cognitive dysfunction in MS (Section 1.1.4).

1.2 COGNITIVE IMPAIRMENT: PATTERN

1.2.1 Characteristic Impairments:

1.2.1.1 General Features:

Generally, the cognitive deficits associated with MS do not impact globally (Rao et al., 1993a), rather, they occur in specific skills, resulting in selective deficiencies. In accordance with the random and unpredictable nature of the disease, there is considerable interpatient variability in both the pattern and severity of cognitive dysfunction in MS (Rao, 1995). It has been observed that patients with MS tend to demonstrate only mild deterioration on standard measures of intelligence (Feinstein, 1995; Rao, 1986; 1995). Likewise, language skills are often relatively well preserved (Franklin et al., 1989; Ron et al., 1991; Achiron et al., 1992), although subtle deficits have been observed (Heaton et al., 1985; Rao et al., 1993a; Kujala et al., 1996b). It has been suggested that naming and reading may be mildly affected in MS, whilst spelling and comprehension remain intact (Jambor, 1969; Caine et al., 1986; Van Den Burg et al., 1987; Rao et al., 1989b; 1991). Abstract or conceptual reasoning is frequently deficient in MS (Parsons et al., 1957; Jambor, 1969; Peyser et al., 1980; Heaton et al., 1985; Rao et al., 1987; 1991; Ron et al., 1991; Mendozzi et al., 1993; Beatty et al., 1995a), as are the skills of sustained attention (Filley et al., 1989; Ron et al., 1991; Rao et al., 1991; DeLuca et al., 1994; Kujala et al., 1995), and visuo-spatial perception (Rao et al., 1991). In addition, the speed of information processing may be compromised (Beatty et al., 1988; Litvan et al., 1988a; Beatty et al., 1989; Rao et al., 1989c; DeLuca et al., 1994; Grigsby et al., 1994; Kujala et al., 1994).

1.2.1.2 Span Of Apprehension:

"Span of apprehension" refers to the amount of information which can be retained in memory long enough for it to be reproduced exactly (McCarthy & Warrington, 1990). It is commonly assessed using the digit span task (Wechsler, 1945; 1955; 1981; 1987), which requires the subject to repeat a string of numbers read aloud at the rate of one per second. The length of the string is incremented by one digit every second trial if at least one string is repeated correctly. A further task, following the same format, requires the subject to repeat the given numbers in the reverse order to that in which they are presented. Intact performance on the digit span task, by patients with MS has been reported by Jambor (1969), Goldstein and Shelly (1974), Staples and Lincoln (1979), Rao et al. (1984), Heaton et al. (1985), Litvan et al. (1988a; 1988b), Rao et al. (1989b), Anzola et al. (1990), Jennekens-Schinkel et al. (1990b), Caltagirone et al. (1991), Klonoff et al. (1991), Pozzilli et al. (1991a), Rao et al. (1991a), Maurelli et al. (1992), and Amato et al. (1995). Conversely, impaired digit span has been recorded by Diers and Brown, (1950), Reitan et al. (1971), Lyon-Caen et al. (1986), Huber et al. (1987), Fischer (1988), Minden et al. (1990), DeLuca et al. (1994), Grigsby et al. (1994), Beatty et al. (1995b; 1995c; 1996), Kujala et al. (1996a; 1997), and Foong et al. (1998).

The two sections of the digit span test, that is digits forward and backward, are usually summated to provide an overall composite score, and this total has been used in the majority of studies cited above. Using the digit span task, Beatty et al. (1995c) examined the performance of 109 patients with MS, relative to 32 matched, healthy controls. They found ability on both digits forward and backward was impaired in the patient group. Although the magnitude of the deficits were comparable for the two

tasks, the patterns of correlations with other neuropsychological tests were distinct. Beatty et al. (1995c) proposed that, in the patient group, the high correlation of digits backward with performance on the short-term memory task supported Lezak (1995), who suggested that the digits backward task was a test of working memory, involving actual processing of the information to be recalled, not simply repetition. Lezak (1995) considered the digits forward section to measure only the efficiency of attention. As the two subtests involve different mental activities, and are affected differently by brain damage, Grigsby et al. (1994), Beatty et al. (1995c), and Lezak (1995) have suggested that performance on digits forward and backward should be analysed independently.

The Corsi span test (Milner, 1971) follows a similar format to the digit span task, but assesses visuo-spatial span of apprehension. The subject must imitate a sequence tapped by the examiner, on a series of nine white cubes. The sequence increases in length if repeated correctly. Using this test, visuo-spatial span memory has been demonstrated to remain intact in patients with MS by Anzola et al. (1990), Caltagirone et al. (1991), Pozzilli et al. (1991a), Maurelli et al. (1992), and Amato et al. (1995). Likewise, Fischer (1988) found the same unimpaired performance on a different visuo-spatial span task. Jennekens-Schinkel et al. (1990b) also recorded preserved ability using the Cube Imitation Test (Knox, 1914). In contrast, Foong et al. (1997) reported deficits on the Corsi span test, and Rovaris et al. (1998) noted that 40% of their patients were categorised as impaired on the same task.

The relationship between so-called 'span memory' and attention is complex; Rao et al. (1984) and Beatty et al. (1995c) both classed the digit span test as a measure of attention, rather than memory. Similarly, Wechsler (1987) in the revised version of the Wechsler Memory Scale, included performance on both the digit span and visual memory span tasks in the calculation of an attention/concentration summary index.

Span of apprehension tests may, however, be considered to measure the capacity of working memory (McCarthy & Warrington, 1990).

1.2.1.3 Working Memory:

Working memory is the temporary storage and processing of information necessary for the concurrent performance of a wide range of cognitive tasks (Baddeley, 1986). Baddeley's (1986) model of working memory comprises a central executive, which regulates verbal and visuo-spatial slave systems that are specialised for different types of temporary storage. The central executive also controls cognitive processing when a novel task is undertaken or when a habitual task must be overridden. Verbal working memory uses a phonological loop, which consists of a limited duration store for phonological codes, called the phonological buffer, and an articulatory rehearsal process, that refreshes the buffer. Visuo-spatial working memory consists of a buffer responsible for the initial registration of nonverbal material, and a visuo-spatial scratchpad, which allows visuo-spatial information to be rehearsed.

The duration of working memory has been assessed by investigating the rate at which material is forgotten in the absence of conscious attention and rehearsal, and is measured by the Brown-Peterson task (Brown, 1958; Peterson & Peterson, 1959). This test involves presenting the subject with a consonant trigram, for example "SPT", followed by a number, such as "891". To prevent rehearsal of the material to be remembered, the subject must repeat the three digit number and then count backwards from it in threes. On being given a signal, the subject is then required to recall the consonants. There have been a number of adaptations to this original task, for example, the use of words instead of consonants.

Grant et al. (1984) found that MS patients when compared with controls, demonstrated deficient working memory, which was particularly vulnerable to the effects of proactive interference. Proactive interference refers to the disruption of learning by previously acquired information; therefore in this case, the target items recalled initially, on the first few trials, interfered with the subsequent learning of novel stimuli. Beatty et al. (1988) also reported deficits in CP MS patients on a variation of the Brown-Peterson task, which used words in place of the consonant trigrams. Beatty et al. (1989) used exactly the same task to examine working memory in RR MS, and noted a poorer performance by their patients, but the results were not significantly different to those of controls. Litvan et al. (1988b), Rao et al. (1989b; 1991; 1993b) all reported normal performance by MS patients on the word variation of the Brown-Peterson task. However, Grigsby et al. (1994) assessed 23 CP MS patients, and found they performed more poorly than controls on the Brown-Peterson task. They commented that on examination of previous research, which used either the Brown-Peterson or digit span tasks, there was a trend in most studies, not necessarily reaching significance, for a deficiency in working memory. Taking these results in the context of the documented deficits in information processing and attention in MS, Grigsby et al. (1994) suggested that the fundamental dysfunction in MS is the deficiency in speed and capacity of central information processing. Span of apprehension may remain intact initially, whilst working memory tasks which involve more complex processing may be compromised.

Using working memory tasks taken from Baddeley's (1986) research, Litvan et al. (1988b), Rao et al. (1993b), and Ruchkin et al. (1994) all recorded results suggestive of a defective articulatory rehearsal mechanism in MS. Ruchkin et al. (1994) also reported that phonological, rather than visuo-spatial working memory may be more vulnerable to disruption by MS. Ruchkin et al. (1994) suggested that the deficiencies in

verbal working memory reported in MS patients may be due to demyelination of the long fibre tracts, such as the superior longitudinal fasciculus, which link the posterior language cortex and anterior speech production cortex (McCarthy & Warrington, 1990; Paulesu et al., 1993). Plaques in the pathways which connect these regions may disrupt the operation of the phonological loop, leading to degraded transmission of information between the posterior phonological buffer and the anterior phonological output system.

D'Esposito et al. (1996) investigated the functioning of the central executive in MS patients using a dual-task paradigm, in which the visual judgement of line orientation was performed concurrently with either finger tapping, humming, or reciting the alphabet. They reported that during the dual-task condition, MS patients exhibited a significantly greater decrement in performance on the primary task (judgement of line orientation) than controls, and proposed that their results reflected an inability of the patient's central executive to allocate sufficient attentional resources to accomplish both tasks effectively. D'Esposito et al. (1996) suggested that, as performance by patients on the dual-task paradigm correlated with their performance on a test of speed of information processing, the findings support Grigsby et al.'s (1994) model.

Thus, it can be seen that span of apprehension and working memory are closely linked to attention and speed of information processing. The degree to which these cognitive skills are impaired in patients with MS remains unclear. Recent research seems to suggest deficiencies in working memory, but their impact, if any, on the functioning of long-term memory is as yet unquantified.

1.2.1.4 Recent Explicit Memory:

Memory function is the most frequently impaired cognitive capability of patients with MS (Rao, 1995; Thornton & Raz, 1997). Neuropsychological research has now demonstrated that not all aspects of memory are uniformly disrupted by MS, with certain facets markedly dysfunctional, while others remain relatively spared (Beatty, 1993; Rao et al., 1993b). When MS patients are asked to recall spontaneously verbal or visuo-spatial information which exceeds their span of apprehension, they are consistently deficient (Beatty & Gange, 1977; Staples & Lincoln, 1979; Grant et al., 1984; Rao et al., 1984; Heaton et al., 1985; Lyon-Caen et al., 1986; Fischer, 1988; Beatty et al., 1988; Litvan et al., 1988b; Beatty et al., 1989; Minden et al., 1990; Rao et al., 1991; 1993b; DeLuca et al., 1994). Subtle recognition memory deficits may also be demonstrated (Rao et al., 1984; Caine et al., 1986; Van den Burg et al., 1987), though not in all studies (Carroll et al., 1984; Rao et al., 1993b). A detailed review of the performance of MS patients on explicit verbal and visuo-spatial tests of recent memory, that is, tasks which employ voluntary processes, assessing knowledge acquired over a relatively brief period, can be found in Sections 1.5, 1.6, and 1.7. The tests used to assess this type of memory in MS are discussed in Sections 1.9 and 1.10.

1.2.1.5 Remote Explicit Memory:

Remote memory, which involves information that was encoded in the distant past has not been extensively studied in MS (Beatty, 1993). Using a test in which past presidents of the United States of America must be named, Caine et al. (1986) recorded a mild impairment in their patient sample, relative to matched controls. In contrast, Rao et al. (1991a) reported no significant difference between the performance of MS patients

and the healthy control group. Beatty et al. (1988; 1989) assessed patients with CP and RR MS, respectively, using a modified version of the Remote Memory Battery (Albert et al., 1979). This test requires the subject to identify famous faces and events from previous decades. In both studies, Beatty et al. (1988; 1989) found patients performed poorly, with a flat temporal gradient, that is, the impairment was equally severe for all decades. Beatty et al. (1988) also administered a revised version of the Fargo Map Test (Beatty, 1988), in which visuo-spatial knowledge of cities and geographical features in the United States of America is assessed. They reported 31% of the patient group as performing below the fifth percentile.

1.2.1.6 Implicit Memory:

Implicit memory refers to the involuntary encoding, storage and retrieval of information. Experimental paradigms have been devised which entail the presentation of information in a way that attempts to exclude voluntary processing or recollection. Such techniques rely on the subject being naïve to the experimenter's intentions, and include tasks such as word stem completion, semantic priming, pursuit-rotor tracking, serial visual reaction time, and mirror reading. Implicit memory has generally been reported to remain intact in MS (Beatty & Monson, 1990; Beatty et al., 1990b; Beatty, 1993; Latchford et al., 1993; Rao et al., 1993b). Unimpaired performance by MS patients on tests of automatic or incidental memory have also been recorded (Grafman et al., 1991).

1.2.1.7 Metamemory:

Metamemory refers to a patient's subjective knowledge about his or her own memory function. Subjective memory reports, by either the individual, a carer, or

clinician, may not concur with the results of formal neuropsychological testing, suggesting that objective tasks may assess different skills from those employed in everyday activities (Baddeley et al., 1982; Hickox & Sunderland, 1992). Nelson et al. (1984) have proposed that in order to make accurate judgements about the state of one's own memory, both access to specific memories and inferential or conceptual mechanisms are required. Beatty and Monson (1991a) found that in their sample of 45 MS patients, those individuals who exhibited problems in recognition memory or conceptual reasoning showed mild deficits in metamemory, while patients with deficiencies in both recognition memory and conceptual reasoning demonstrated extensive dysfunction of metamemory. Likewise, Kujala et al. (1996a) who recorded 23 of their 45 MS patients as significantly impaired on objective memory tests, found those same individuals reporting more difficulties in everyday memory function, that is, their self-evaluation of their memory and learning problems was accurate. However, self-report is not necessarily a reliable measure, being subject to the 'memory introspection paradox' (Herrmann, 1982). This refers to the notion that individuals most likely to suffer memory deficits are also those most inclined to forget such failures, and so fail to report them.

Alternatively, carers or relatives may detail patients' memory function. McIntosh-Michaelis et al. (1991) found that 44% of their MS sample reported memory dysfunction, of whom 38% actually demonstrated objective memory deficits. In contrast, of those patients who performed very poorly on objective memory assessments, 81% of the relatives reported memory difficulties in the patient. Despite this evidence, carer report may be biased, as only observed memory failures can be detailed (Hickox & Sunderland, 1992). The carer can only report on the status of the memory capabilities demonstrated by the patient in their presence. This account may not

provide a comprehensive representation of memory function, as the patient may attempt to conceal deficits, or avoid situations where there is the potential for weakened skills to be exposed.

Thus, it can be seen that patients with MS regularly demonstrate deficits in conceptual or abstract reasoning, attention, speed of information processing, and visuo-spatial skills. Controversy surrounds a number of cognitive capabilities where conflicting results have been reported. Studies examining span of apprehension and working memory in patients with MS have yielded inconsistent findings, as have those assessing recent explicit recognition memory, and remote explicit memory. Several authors have reported impaired recent explicit recall memory and metamemory in MS patients, whilst implicit memory, and automatic or incidental memory appears to remain intact. A definitive profile of cognitive dysfunction in MS is, however, unlikely due to the diffuse pathology of this demyelinating disease.

1.2.2 The Progression Of Cognitive Dysfunction: Evidence From Cross-Sectional Studies At Different Stages Of The Disease

1.2.2.1 Cognitive Dysfunction As A Presenting Symptom Of MS:

Russell (1964) noted that the absence of physical signs of cerebral involvement is not necessarily indicative of exclusion, as cerebral involvement may occur insidiously, that is, there may be clinically silent lesions. These plaques may later manifest as dementia, and there are a small number of cases in the literature where MS patients present with the features of general dementia, and are concurrently or subsequently diagnosed with MS. Bergin (1957) detailed two cases in whom the rapid onset of dementia was the main clinical feature, and the diagnosis of MS was

subsequently confirmed. Likewise, Koenig (1968) reported seven male subjects in whom dementia was the predominant clinical characteristic. Although six of the group exhibited concomitant neurological symptoms, their most striking symptom was their global cognitive dysfunction. Young et al. (1976) also recorded patients (N=5) whose mental changes were a prominent aspect of their MS, again occurring in conjunction with clinical signs of brain stem involvement. More recently, Fontaine et al. (1994), detailed two female patients with histologically confirmed MS, who presented with progressive cognitive deterioration, while Hotpof et al. (1994) reported two male patients who presented with progressive dementia, in the absence any substantial neurological signs or symptoms, but using MRI, cerebrospinal fluid analysis, and electrophysiological findings, were subsequently diagnosed with MS. Mendez (1995) also reported two cases, both of whom presented with a dementing illness, and were subsequently confirmed to have MS.

These uncontrolled, clinical case studies of progressive global cognitive impairment in the absence of other neurological symptoms are rare, but illustrate how cognitive dysfunction may be an early or presenting symptom of MS. The diagnosis of MS should also be reviewed if patients exhibit progressive dementia, but only minimal physical disability, over time. Fox et al. (1989) recorded two patients in whom the diagnoses of MS were re-evaluated, and a third who had never been formerly diagnosed, despite supporting evidence from laboratory investigations and clinical examinations. The physical disability of the patients had remained mild and stable over many years, yet all demonstrated marked progressive cognitive deterioration. Following a careful review, the diagnoses of the two patients were confirmed, and the third individual was given a definite diagnosis of MS. Filley et al. (1989) and Franklin et al. (1989) have also commented on the significance of dementia in patients with MS.

1.2.2.2 Cognitive Dysfunction And Clinically Isolated Syndromes:

The initial presentation of optic neuritis, brain stem, or spinal cord syndromes, that is, clinically isolated syndromes (CIS), are frequently the harbingers of MS (Francis et al., 1987; Miller et al., 1989). Even prior to diagnosis of MS, some cognitive deficits have been demonstrated in controlled group studies of CIS patients. Lyon-Caen et al. (1986) demonstrated significant cognitive deficits in six of their nine patients with optic neuritis, when compared with a control group of patients with other neurological conditions, namely; headache, epilepsy, and facial palsy. Similarly, Callanan et al. (1989) who compared a group of 48 CIS patients with 46 patients with rheumatological and neurological conditions not known to cause brain disease, found the patients with CIS showed deficits in IQ, and auditory and visual attention relative to the controls. Ormerod et al. (1987) have noted that at presentation, over half of patients with CIS demonstrate MRI pathology elsewhere in the brain. Consistent with this finding, Feinstein et al. (1992a), when examining a sample of 42 patients with acute optic neuritis, reported 55% as showing cerebral lesions on MRI. Feinstein et al. (1992a) compared the performance of patients and matched, healthy controls on a battery of tests of attention and information processing speed. They found that the patients with brain abnormalities were more cognitively impaired than those without lesions, or the normal control group. Additional research into the development of the cognitive deficits associated with MS is provided by Feinstein et al. (1992b), who conducted a four and a half year follow up of the 48 CIS patients assessed in the Callanan et al. (1989) study. On re-examination of the sample, which was reduced to 35 patients, it was noted that 19 of the group had developed clinically definite MS. These patients demonstrated visual memory deficiencies, and, on division into those with RR and CP subtypes, the latter

group were found to have significantly deteriorated on the additional measures of immediate and delayed story recall, paired associate learning, and auditory attention.

1.2.2.3 Cognitive Dysfunction And Clinically Definite MS:

The cognitive deficits of patients with CIS are generally mild. However, they may be the prelude to a pattern of deterioration (Ron et al., 1991). Ron et al. (1991) reported the cognitive impairments of a sample of 58 MS patients, relative to 46 physically disabled controls without significant brain disease. The MS patients demonstrated deficits in IQ, memory, abstracting ability, and visual and auditory attention, relative to the control group. Ron et al. (1991) compared their data with that of Callanan et al. (1989) and noted that, with respect to cognitive impairment, patients with CIS appear to occupy an intermediate position between MS patients and physically disabled control subjects, in terms of the severity of cognitive dysfunction.

Patients with RR MS have been reported to demonstrate significant cognitive dysfunction. Klonoff et al. (1991) assessed the neuropsychological performance of 86 RR MS patients who were in remission, relative to that of 46 matched, healthy controls. They found the patient group were significantly impaired on learning and memory tests, when compared with the controls. This study would suggest that although patients with RR MS have been reported to show improved cognitive performance in parallel with neurological recovery from a relapse (Rozewicz et al., 1996), residual deficits may remain, even during the early stages of the disease process.

Many researchers have noted that cognitive function appears to decline with the progression of the disease (Heaton et al., 1985; Beatty et al., 1989). There is evidence to suggest that while RR patients show mild to moderate forms of impairment, CP patients

demonstrate more severe deficiencies (Heaton et al., 1985; Beatty et al., 1989). Heaton et al. (1985) examined the neuropsychological functions of 43 CP and 57 RR MS patients, and found that the RR group showed much less cognitive impairment, with almost one third of patients maintaining normal neuropsychological skills. In contrast, 98% of the CP patients demonstrated some form of cognitive deficiency. Beatty et al. (1988) investigated cognitive disturbances in 38 patients with CP MS. They reported marked impairments in information processing, verbal fluency, anterograde memory, and problem solving. In a similar study with 42 RR MS patients, Beatty et al. (1989) recorded the same pattern of deficits, but commented that the severity of the impairments was reduced.

Comi et al. (1995) contrasted the cognitive capabilities of 14 PP patients and 17 patients with SP MS. Using a criteria of impairment based on published norms (more than two standard deviations below the published control mean on three or more tests), they found that only 7% of the PP group, compared with 53% of the SP patients, demonstrated significant cognitive impairment. The groups were of similar age and disability, but the SP patients recorded longer disease durations. Comi et al. (1995) suggested that the smaller incidence of cognitive impairment in PP MS related to the lower cerebral MRI lesion loads of these patients. However, in a recent study of 63 PP and TP MS patients, compared with individually matched, healthy controls, Camp et al. (1999) recorded significant deficits in the patient group on tests of verbal memory, attention, verbal fluency, and spatial reasoning. To provide a broad comparison with the Comi et al. (1995) paper, as the demographic and clinical characteristics of the PP patient samples were similar, Camp et al. (1999) adopted a close approximation of the Comi et al. (1995) criteria of cognitive impairment; 28.6% of the patients were classed as demonstrating significant cognitive dysfunction. Thus it would appear from this latest

cross-sectional study that PP and TP patients, like other subgroups of the MS population, demonstrate significant cognitive impairment.

On examination of cross-sectional, controlled, neuropsychological group studies, which assess patients on only one occasion, but at varying stages of the disease process, it would appear that cognitive dysfunction is a relatively common feature of MS, regardless of disease type, duration, or level of disability. From the studies conducted at different time points throughout the disease process, it would appear that the pattern of cognitive deficits intensifies as the disease progresses. Attention and speed of information processing are the most notable deficiencies in patients with CIS. Impaired memory function, deficits in abstract or conceptual reasoning and visuo-spatial perception, and a decrease in attentional and information processing skills characterise the pattern of cognitive dysfunction in MS patients. Deterioration of these deficiencies appears to continue as the demyelination advances. However, longitudinal studies of patients with MS have not provided unequivocal support for this hypothesis.

1.2.3 The Progression Of Cognitive Dysfunction: Evidence From Longitudinal Studies

A number of researchers have shown no change in the cognitive skills of MS patients over time. Fink and Houser (1966) examined 44 patients with recent onset MS. They conducted a one year follow-up, and noted that patients had improved on the verbal sections of the Wechsler Adult Intelligence Scale (Wechsler 1955). Ivnik (1978b) also showed relative preservation, or only very mild deterioration, after one year, in the cognitive performance of 14 MS patients relative to 14 matched, non MS, neurological controls. Filley et al. (1990) followed 46 patients for a mean of 18.8 months and demonstrated preservation of cognitive skills over this period. Likewise, Jennekens-

Schinkel et al. (1990a) conducted a four year follow-up of 33 MS patients and 18 healthy controls. They found preservation of cognitive function in 76% of their patient group. Mariani et al. (1991) noted similar findings in 19 RR patients reassessed after two years, as did Mattioli et al. (1993) with nine patients after three months. Amato et al. (1995) conducted a four year follow-up of 50 patients with early onset MS, and 70 demographically matched, healthy controls. They reported that the cognitive deficits of verbal memory and abstract reasoning identified at the initial assessment remained comparatively stable over the follow-up period, with supplementary linguistic deficits emerging at the second assessment. Hohol et al. (1997) examined 44 MS patients after one year, and found no decline in cognitive performance.

In contrast to these studies which demonstrated preservation of cognitive skills over time, Canter (1951) identified a significant drop in IQ in 23 males, who were reassessed after four years. He also found the same pattern of deterioration in 47 MS patients relative to 38 matched controls after a six month follow-up period. Feinstein et al. (1992b), as previously detailed (Section 1.2.2.2), have shown cognitive deterioration in their longitudinal study, with a follow up period of four and a half years. Feinstein et al. (1993) conducted another serial study, following 5 patients with RR MS, and 5 individuals with benign MS. Cognitive tests were administered every two or four weeks, and Feinstein et al. (1993) reported that in those individuals with active disease, cognitive performance on tests of attention and information processing deteriorated or failed to demonstrate the practice effects of the controls. In the most comprehensive study to date, Kujala et al. (1997) examined 42 MS patients and 34 healthy controls. They found that, after three years, those individuals who were cognitively intact at baseline (N=20) showed substantial neuropsychological stability, performing as well as

the controls at follow up; whereas those patients who were initially impaired (N=22) demonstrated progressive cognitive decline.

Control groups are very important in longitudinal studies to monitor the impact of practice effects on cognitive task performance. Perhaps the contrasting findings in this area may be due partly to the lack of control subjects in some studies, and partly to the varying sensitivities of neuropsychological tests in identifying significant change in performance. In addition, some MS patients may not experience cognitive change over the time scales which have been studied.

1.2.4 Summary:

- Patients with MS demonstrate deficits in abstract reasoning, speed of information processing, attention, visuo-spatial skills, recent explicit recall memory, and metamemory. Studies examining span of apprehension, working memory, recent explicit recognition memory, and remote explicit memory have produced conflicting findings (Section 1.2.1).
- Single case studies have illustrated that cognitive dysfunction may be an early or presenting symptom of MS. Cross-sectional, controlled, neuropsychological group studies of patients at various stages of the disease (CIS, RR MS, & CP MS), have demonstrated that cognitive deficiencies may occur early in the disease process, and appear to intensify as the disease progresses (Section 1.2.2).
- Despite these findings, longitudinal studies of patients with MS do not provide unequivocal support for the deterioration of cognitive functions with disease progression (Section 1.2.3).

1.3 COGNITIVE IMPAIRMENT: SUBCORTICAL DEMENTIA

1.3.1 The Concept Of Subcortical Dementia:

The pattern of cognitive deficits exhibited by MS patients has been noted by Rao (1986) to be similar to that of other diseases categorised as subcortical dementias. Subcortical dementia is characterised by personality disturbances such as apathy or depression, memory retrieval failure with relatively intact encoding and storage capacity, deficient conceptual/abstract reasoning, and slowed information processing (Albert et al., 1974; Albert, 1978; McHugh & Folstein, 1975; Cummings & Benson, 1984). Disorders classified as subcortical dementias primarily exhibit pathological changes in the thalamus, basal ganglia, and related brain stem nuclei. They include Huntington's Disease (HD), Parkinson's Disease (PD), and progressive supranuclear palsy. In contrast, cortical dementia can be identified by severe amnesia, specifically encoding deficits, agnosia, acalculia, and aphasia (Cummings & Benson, 1984). Alzheimer's Disease (AD) is a common example of a cortical dementia.

In order to demonstrate the neuropsychological similarities or differences between patients with distinct neurological diseases, many studies have used the Mini Mental State Examination (MMSE; Folstein et al., 1975), a brief assessment of cognitive function. However, not only is the MMSE insensitive to cognitive dysfunction, but it is also has methodologically limitations (Section 1.1.1). Mayeux et al. (1983), using a modified version of the MMSE (Folstein et al., 1975; Mayeux et al., 1981), failed to find significant differences in the cognitive performance of AD (N=46), PD (N=57), and HD (N=20) patients, compared at three functional stages of disability. They therefore considered the notion of subcortical dementia to be misleading, as the

profile of neuropsychological deficits found in AD, HD, and PD patients appeared similar, and may be the result of combined cortical and subcortical degeneration.

Further criticism of the subdivision of dementia was made by Whitehouse (1986), who disputed the separation into subcortical and cortical dementia on anatomical grounds. Autopsy studies have indicated that pathological changes in diseases such as HD, PD, and AD, are not restricted to either cortical or subcortical regions (Bruyn et al., 1979; Whitehouse et al., 1981). Cortical pathology associated with the clinical features of subcortical dementia has been documented in both PD and HD (Victor, 1978; Boller et al., 1980). Likewise, subcortical lesions may be significant in the pathogenesis of AD (Whitehouse et al., 1981; Katzman, 1986). In addition, Whitehouse (1986) noted that it remains unclear whether common features of 'cortical dementias' are sufficiently distinct from those of 'subcortical dementias'. In available comparison studies of these different dementias, various criteria for diagnosis are often employed. Moreover, characterisation of clinical symptoms may be difficult, and matching patients often proves problematic.

In favour of subcortical dementia as a separate entity, Kuhl et al. (1982) found significant hypometabolic activity in the caudate and putamen, but not in the cerebral cortex of HD patients. In addition, some researchers have provided neuropsychological support for the concept of subcortical dementia. Salmon et al. (1989) and Brandt et al. (1988) demonstrated differences in the cognitive profiles of AD and HD patients, as did Huber et al. (1989) between AD and PD patients.

It has been argued that implicit memory dysfunction may be a feature of subcortical dementia, with intact ability a characteristic of cortical dementia. Deficits in implicit memory function have been demonstrated in patients with HD (Martone et al., 1984; Heindel et al., 1988). However, Weingartner et al. (1984) and Shimamura et al.

(1987) did not find this impairment in PD and HD patients, respectively. Nebes et al. (1984), Eslinger and Damasio (1986), and Heindel et al. (1988) all reported that patients with AD exhibited a normal capacity for implicit memory, although Shimamura et al. (1987) and Salmon et al. (1988) recorded deficient priming in AD patients.

Thus, despite the apparently distinct characteristics of subcortical dementia detailed above, diseases classed as subcortical dementias form a heterogeneous group, with diverse cognitive impairments (Lundervolv et al., 1994; Troster et al., 1998). It appears that empirical support for the concept of a cortical/subcortical distinction may be inadequate.

1.3.2 MS As A Subcortical Dementia:

If the concept of subcortical dementia is accepted, it has been suggested that MS should be included, because of the location of the majority of MS plaques, and the profile of cognitive deficiencies in MS patients (Rao, 1986). Pathological support for this categorisation comes from studies which have demonstrated that MS is primarily localised to subcortical periventricular white matter (Raine, 1990), leading to disruption of synaptic transmissions between subcortical structures such as the thalamus, the basal ganglia, and related brain stem nuclei. However, recent research has shown cortical lesions to be more frequent than might be predicted clinically (Kidd et al., 1999). Neuropsychological research reporting the lack of focal 'cortical' signs, the pattern of memory loss, the conceptual reasoning deficits with relatively spared intellect, and the intact language capabilities of MS patients, has also been cited as supporting the inclusion of MS within the group of diseases classed as subcortical dementias.

Caine et al. (1986) conducted a study comparing the neuropsychological deficits of 21 patients who presented with the earliest stages of HD, with those of 30 RR MS patients. The groups were matched for age, education, and level of disability. Despite the patient samples showing similar overall patterns of cognitive impairment on a range of neuropsychological tests, the HD patients demonstrated greater verbal and visuo-spatial memory deficits, significant dyscalculia, and mild problems in language usage and copying. Caine et al. (1986) considered these discrepancies to "reflect the fundamental differences in the neuropathology of the two distinct diseases".

Beatty et al. (1988) noted that their sample of 38 CP MS patients demonstrated memory disturbances and slowed information processing, deficits typically observed in subcortical dementia. The slowed information processing illustrated on the Symbol Digit Modalities Test (Smith, 1973), the deficits in verbal fluency, and the pattern of failures on the Brown-Peterson task (Brown, 1958; Peterson & Peterson, 1959), closely corresponded to deficiencies found in HD patients (Beatty et al., 1986). Likewise, the deficits in verbal memory, where recall was more impaired than recognition, have been documented in HD (Butters et al., 1985; 1986). In a comparison of the verbal memory performance of HD and MS patients, conducted by matching the MS subjects with HD patients (Beatty et al., 1986) according to recall level, it could be seen that delayed recognition performance was almost identical, with respect to the number of target words detected, the percentage correct, and the number of false positives. Beatty et al. (1988) also recorded a flat temporal gradient of remote memory in their CP MS patients, which has been reported in HD and PD patients (Albert et al., 1981; Freedman et al.,1984; Huber et al., 1986a). These findings advocate a qualitative similarity between MS and HD or PD, both of which may be thought of as subcortical dementias. Despite the support for MS as a subcortical dementia provided by this study, naming difficulties

were reported in the MS patient group, and there was an increase in the number of perseverative errors on letter and category fluency tests. Naming remains intact, or is only marginally impaired in HD or PD patients (Joiassen et al., 1978; Huber et al., 1986b). Moreover, both anomia and perseverations have been noted to be associated with cortical dementia (Beatty et al., 1986; Butters et al., 1987). Beatty et al. (1988) remarked that CP MS patients have a profile of deficits which appears to share features of the cognitive disturbances found in both subcortical and cortical dementia. They suggested that this concurs with the pathology of MS, where lesions may compromise transmission in both cortical and subcortical pathways (Brownell & Hughes, 1962; Lumsden, 1970).

Beatty et al. (1989) reported a pattern of cognitive deficits in a group of patients with RR MS which was consistent with the concept of subcortical dementia. The patient sample demonstrated slowed information processing, poor verbal fluency, anterograde memory deficits that were significant only for recall not recognition, remote memory deficiencies, and impaired problem solving capabilities, with an increase in perseverative responses and nonperseverative errors. Beatty et al. (1989) suggested that their results in patients with RR MS appeared to offer strong support for Rao's (1986) hypothesis. Despite this proposal, they commented on the idiosyncrasy of individuals' cognitive profile, noting that, although the group data indicated a pattern of cognitive deficits consistent with subcortical dementia, few patients on their own demonstrated all the relevant features.

Rao et al. (1989b) also provided support for the notion of MS as a subcortical dementia, emphasising the similarities between the memory impairment of HD and MS patients. They reported deficient long-term memory and verbal fluency, yet intact working memory, recognition memory, and rate of forgetting from long-term memory,

in 37 MS patients. Although the study was not designed as a direct comparison with another patient group, Rao et al. (1989b) attempted to put their results in the context of other research. They noted that as with MS patients, HD patients show normal working memory capacity, yet deficient long-term memory (Wilson et al., 1987a), and that this contrasts with AD patients who exhibit defective working memory (Kaszniak et al., 1986). Moreover, Butters et al. (1986) reported near normal recognition memory but deficits on fluency tests in patients with HD, as Rao et al. (1989b) illustrated in their MS group. The impaired recall memory, but intact recognition, suggested that the memory dysfunction in MS may be due to problems with retrieval, again consistent with subcortical dementia. Huber et al. (1987) reported a pattern of cognitive abnormalities compatible with subcortical dementia in a group of 32 patients with MS. Likewise, Rao et al. (1991a) recorded similar findings in a sample of 100 community-based MS patients.

The cognitive profile of MS patients has also been examined relative to that of patients with cortical dementia, namely, AD. Filley et al. (1989) compared 42 AD patients with an equal number of individuals with CP MS, on a broad neuropsychological test battery. AD patients illustrated a greater impairment of learning, memory, visuo-spatial function, and verbal skills, with limited sensory or motor deficits, whilst MS patients were more impaired on attention, incidental memory, and psychomotor tasks. Filley et al. (1989) reported AD and MS patients as showing distinct neuropsychological features, which may be dictated by the different neuropathological involvement of the diseases. AD involves neuropathological degeneration in predominantly grey matter, whilst MS is characterised by demyelinating lesions in the white matter. Although their study provides qualified support for MS as a subcortical dementia, Filley et al. (1989) suggested that as the cortical-subcortical dichotomy is

confounded by ambiguous neuropathological differences, a distinction between grey matter and white matter dementias may be a more perceptive division for categorising such disorders. However, even this separation is not complete, there may be some degeneration in the optic nerve of AD (Hinton et al., 1986) and grey matter plaques may occur in MS (Brownell & Hughes, 1962; Kidd et al., 1999).

Deficient implicit memory has been suggested as a feature of the diseases which may be thought of as subcortical dementias. Beatty and Monson (1990) and Beatty et al. (1990b) found no impairment on the implicit memory tasks of stem completion and pursuit rotor learning in MS patients. Likewise, Latchford et al. (1993) who examined 12 RR MS patients using an explicit verbal free recall and recognition memory test, and stem completion of the same word list as the implicit memory task, found no significant impairment of implicit memory, but deficits in explicit recall memory. Rao et al. (1993b) have also reported normal performance in 46 MS patients on two implicit memory measures; the serial visual reaction time test, a motor learning task; and mirror reading, a skill acquisition test.

These results are incompatible with those recorded in some studies of patients with HD (Martone et al., 1984; Heindel et al., 1988), but do concur with those reported in others, which examined HD and PD patients, respectively (Weingartner et al.,1984; Shimamura et al., 1987). The inconsistencies in the literature may be reconciled by Coltheart (1989), who suggested that implicit memory may comprise more than one system, that such systems may be dissociable, and that it may be possible to impair selectively one subsystem (Bondi & Kaszniak, 1991). Deficits in priming may result from damage to the association cortex of the language dominant hemisphere, which limits access to the representations of lexical memory. Conversely, impairments in learning visuo-motor skills may be a consequence of damage to the neostriatum

(Shimamura et al.,1987; Butters et al., 1988a; Salmon et al., 1988). These findings suggest that variety in task type may lead to the selective dysfunction of certain forms of implicit memory in cortical and subcortical dementias.

It would appear, therefore, that there is much controversy over the inclusion of MS within the category of subcortical dementia, with pathological and neuropsychological evidence, which both supports and refutes the notion. Beatty et al. (1990b) considered the pattern of cognitive impairment in MS to be unique and not prototypical of either cortical or subcortical dementia. It has been suggested that "white matter dementias" may possess neurobehavioural features, which are distinct from the subcortical dementias that involve predominantly grey matter structures, and that this may be a more discerning categorisation (Filley et al., 1989).

1.3.3 Summary:

- Controversy remains around the concept of subcortical dementia as a separate entity. There is conflicting pathological and neuropsychological evidence regarding the cortical/subcortical division of dementia (Section 1.3.1).
- The pattern of cognitive dysfunction exhibited by patients with MS, together with knowledge of the pathology of the disease, do not offer unequivocal support for the inclusion of MS within the category of subcortical dementia (Section 1.3.2).

1.4 PROBLEMS OF TESTING MEMORY IN MS

MS lesions in the brainstem, cerebellum, and spinal cord, can interrupt sensori-motor afferent and efferent systems without necessarily affecting the higher cognitive functions. However, scores on memory measures which require competent sensori-motor skills may be prejudiced by physical disability, leading to an imprecise assessment of capability. Coexisting cognitive deficits may also impact negatively on patients' performance on memory tests for which intact global processing is a necessity. In addition, to obtain a comprehensive measure of memory in patients with MS, there are a number of methodological issues relevant to the structure of a memory assessment which need to be addressed.

1.4.1 Physical Handicaps:

The most usual, initial, clinical manifestations of MS are sensory (40%), visual (35%), motor (21%), brain stem (16%), or cerebellar (15%), and although symptoms due to disruption of these systems may remit, residual deficiencies often persist (Fieschi et al., 1997). Hence, neuropsychological skills, even during the early course of MS, may be assessed concurrent with physical disability. Throughout the disease process, the measurement of cognitive abilities, such as memory, is confounded by the physical impairments of the patient, which compromise the sensori-motor functions on which the majority of neuropsychological tasks rely.

Dysarthria, that is, impaired and slurred speech, is a common characteristic of MS, which is due to spastic weakness and/or ataxia of the muscles of articulation. Dysarthria may prejudice a patient's cognitive performance if the task requires a spoken response. Unfamiliar and polysyllabic words will be difficult for a patient in whom

laboured or inarticulate speech is a prominent feature. For example, in a verbal free recall task, processing resources may be diverted away from remembering the items and focused on the pronunciation of the stimuli, thus creating a bias towards poor performance.

Patients with MS may be also be affected by cerebellar ataxia, intention tremor, chronic pain, spasticity, or sensory disturbances, all of which may compromise upper limb function. In these patients manual dexterity is limited, preventing accurate completion of fine motor tasks, such as drawing. Visuo-spatial free recall tasks often require the patient to draw stimuli from memory. Reproductions may be imprecise due to the subject's inability to hold and/or move the pencil as intended, resulting in a distorted score on the memory assessment.

Visual disturbances, for example, optic neuritis, oscillopsia, opsoclonus, diplopia, loss of brightness, indiscriminate colour vision, altered depth perception, and poor visual acuity, are a common feature of MS. Patients with visual difficulties may be penalised on conventional memory tests, where unimpaired vision is a prerequisite. Visuo-spatial recall and recognition tasks frequently require fine details to be retained; if these have not been seen, and hence not encoded initially, they will, by definition, never be retrieved, thus cognitive performance will automatically be negatively biased.

1.4.2 Supplementary Cognitive Dysfunction:

In addition to their physical disabilities, MS patients may also exhibit coincident cognitive deficits, for example attentional or perceptual dysfunction, which will affect performance on memory tasks. Restricted aural presentation is employed in several conventional verbal memory assessments; this will be problematic for a patient with

attentional deficits, as attending to the stimuli is an essential staging post to memory. Likewise, perceptual disorders create inherent problems for visuo-spatial memory tasks, as the stimuli must be correctly perceived in order that the processes involved in memory can be assessed.

1.4.3 Methodological Issues:

There are additional problems of testing memory in MS which are technical shortcomings of the neuropsychological measures used, rather than difficulties due to the coincident disabilities of the patient group. One complication is that neuropsychological tests seldom span the entire range of ability. Memory skills in MS patients may remain intact, or they may be severely impaired. Ideally, a measure of memory should be capable of adequately assessing all sections of the ability spectrum, without evincing pronounced floor and ceiling levels, although in practice this may not prove feasible. The floor effect refers to the situation where a large number of subjects score the lowest possible score on a given test. However, the assessment tool cannot discriminate between the different levels of ability at the impaired end of the spectrum. A similar principle applies to the ceiling effect, that is, where several subjects achieve the highest score, and again the measure is incapable of distinguishing differences in ability, at this end of the range.

When comparing verbal and visuo-spatial memory capabilities, and different forms of memory for a given subject, the formats and content of the tasks are typically unmatched, therefore, there is a possibility of systematic bias resulting from test artefacts. Artefacts due to the varied structure of cognitive tests cannot be precisely predicted and may be a source of error. Presentation and response mode for either verbal

or visuo-spatial memory tests may differ and differentially bias performance. Content artefacts are also difficult to quantify: visuo-spatial memory tests may utilise novel, more unusual stimuli than verbal assessments, and, therefore, there may be a discrepancy in the saliency of the items.

1.4.4 Summary:

- Physical disability may influence memory test performance if the neuropsychological assessment relies on efficient physical function. Cognitive test scores may be negatively biased by poor speech, visual disturbances, and/or compromised manual dexterity, if such skills are a prerequisite for task completion (Section 1.4.1).
- In addition, coincident cognitive deficits may adversely impact on the measurement of memory. Attentional deficiencies and perceptual disturbances may automatically penalise patients on assessment tools which require intact, global, cognitive ability (Section 1.4.2).
- Design issues must also be addressed when developing a new measure. The assessment should attempt to minimise format and content artefacts, and endeavour to grade ability across the spectrum (Section 1.4.3).

1.5 MEMORY FUNCTION IN MS: RECALL MEMORY

Recall memory is the ability to retrieve verbal or visuo-spatial information from memory without cues or prompts. It is the most challenging form of memory function because details must be retrieved unaided from the store. Deficits in recall memory indicate problems with any or all of the encoding, storage, and retrieval processes which constitute memory. There are both immediate and delayed assessments of recall memory, however, caution must be applied when interpreting results: if a patient demonstrates deficient performance on the immediate free recall trial of a memory test, delayed recall will necessarily be weak, due to the reduced amount of information initially encoded. Numerous studies have examined recent explicit recall memory in patients with MS, hence patients with different forms of the disease, at various levels of disability, and with varying disease durations, have been assessed using a variety of neuropsychological assessments. Details of the tests used in the following studies of patients with MS can be found in Sections 1.9 and 1.10.

1.5.1 Verbal Memory:

Verbal recall memory may be assessed using list learning tasks and story recall tests. Supraspan word lists are presented to the subject, who is then required to recall as many items as possible. Story recall tests entail the presentation of a brief passage to the subject, who must then recount as many details as he or she can remember. Although story recall tasks examine verbal free recall memory, they are not as pure a measure as the list learning tests; language skills form an integral part of the assessment, and performance may be enhanced by reconstructing the story from schema. Scoring a story recall test also creates difficulties; because few subjects repeat exactly what has been

presented, the examiner must decide how pronounced alterations, substitutions, omissions, and elaborations must be to warrant loss of points.

1.5.1.1 List Learning Tasks:

Jambor (1969) demonstrated a significant immediate verbal recall memory impairment in 103 MS patients, relative to 79 demographically matched (i.e. for sex, age, and education) controls. However, there was no significant difference between the performance of the MS patients and that of 37 unmatched patients with muscular dystrophy. Beatty and Gange (1977), using 26 patients with MS and 26 demographically matched controls, found that the MS patients performed more poorly than the controls on a list learning test.

Rao et al. (1984) assessed 44 patients with CP MS on a free recall list learning test, which included both immediate and 30 minute delayed recall trials. The patients performed significantly below the 15 demographically matched, healthy controls, and 23 chronic pain patients, who were also matched for medication usage. Caine et al. (1986) noted significant deficits of immediate and 10 minute delayed verbal free recall. The patient group comprised 30 individuals with MS, compared with 15 age and education matched controls. Van den Burg et al. (1987) investigated free recall memory using a list learning test, in a sample of 40 MS patients, relative to an equal number of sex, age, and education matched controls. They noted a significant impairment in both the immediate and 25 minute delayed assessments. Litvan et al. (1988b) also reported deficiencies in verbal free recall memory, in a sample of 16 patients with MS, compared with an equal number of demographically matched controls. They found a significant impairment of immediate and 30 minute delayed recall memory. Beatty et al. (1988)

detailed deficits in immediate and 30 minute delayed verbal free recall memory in a sample of 38 CP MS patients, relative to 26 age and education matched controls. They subsequently found similar results in a group of 42 RR subjects, when compared with 24 demographically matched, healthy individuals (Beatty et al., 1989). These deficiencies were, however, less pronounced than in the CP patient group. Rao et al. (1989b) investigated the memory deficits of 37 MS patients, comparing them with the abilities of 26 controls, matched for age, education, and verbal intelligence. On a word list recall task, the patient sample performed significantly worse at both the immediate and one hour delayed assessments.

Jennekens-Schinkel et al. (1990b) assessed 39 MS patients and 24 controls matched for socio-economic status. They reported a dysfunction in both the immediate and 30 minute delayed recall of words presented aurally to the subject, and deficits in only the 60 minute delayed recall assessment of a word list presented visually. Minden et al. (1990), who examined 50 MS patients, relative to 35 sex, age, and education matched controls, noted significant verbal free recall memory impairment on both immediate and 20 minute delayed trials. Pozzilli et al. (1991a) assessed 17 MS patients, and an equal number of demographically matched, healthy controls. They found deficits in immediate and 15 minute delayed verbal free recall memory. Rao et al. (1991a) reported similar findings in a community sample of 100 MS patients and 100 demographically matched controls. Patients were significantly impaired, relative to controls, on the immediate assessment of a word list. Maurelli et al. (1992) assessed 34 MS patients, and 18 age and education matched controls, on a list learning task. They found patients were significantly more impaired than controls on both immediate and 20 minute delayed assessments. Likewise, Swirsky-Sacchetti et al. (1992b) recorded 41% of their 40 MS patients as exhibiting deficits of verbal recall memory. They used

established cut off scores to categorise impairment, and assessed patients immediately, and after a 20 minute delay. Rao et al. (1993b) reported patients as significantly impaired on the immediate recall of a word list. The patient group comprised 46 MS patients, compared with 47 demographically matched, healthy controls. Likewise, Filippi et al. (1994) examined 42 MS patients, and reported that 17% of patients were impaired (i.e. scored below the fifth percentile of the normal population) on a list learning test. Beatty et al. (1995b) reported immediate and 30 minute delayed verbal recall memory impairment in 103 MS patients, relative to 32 demographically matched controls. Amato et al. (1995) assessed list learning free recall memory in 50 MS patients and 70 sex, age, and education matched healthy controls. They found no significant difference between the two groups on the immediate assessment, but patients performed significantly worse following both a 10 minute and 24 hour delay. Comi et al. (1995), using established cut offs to define cognitive impairment, found 13% of their 31 MS patients were impaired on a list learning task. Similarly, Armstrong et al. (1996) who assessed 67 MS patients, relative to 22 age and education matched controls, found patients were impaired on an immediate verbal free recall task. Beatty et al. (1996) reported significant immediate and 30 minute delayed verbal recall memory impairment in 99 MS patients, when compared with 32 demographically matched controls. Kujala et al. (1996a) examined 45 MS patients and 35 healthy controls. Patients were impaired on the immediate assessment of a list learning task. Similarly, Rovaris et al. (1998) recorded 63% of their 30 patients with MS as impaired on a free recall test. Camp et al. (1999) compared 63 patients with PP and TP MS, with 63 individually matched, healthy controls, and noted patients were significantly impaired at both immediate and 11 minute delayed assessments. 19% of the patient group were categorised as impaired on

both trials, where impairment was taken as obtaining a score more than two standard deviations below the control mean.

1.5.1.2 Story Recall Tasks:

Staples and Lincoln (1979) assessed 64 patients with MS, and, by reference to published norms, found the patients to be significantly impaired on both the immediate and 20 minute delayed story recall tasks. However, when comparing 29 of these patients with an equal number of patients with muscular dystrophy, matched for age, sex, and socio-economic status, there was no significant difference between the two groups. Grant et al. (1984) researched 43 patients in the early and middle phases of MS (mean number of years of active disease 4.47 ± 3.56). They noted disturbances of verbal learning and 45 minute delayed recall memory in the MS group, relative to 28 demographically matched, healthy controls. Rao et al. (1984) also noted deficient story recall memory, in MS patients, relative to matched chronic pain patients and healthy controls. They tested subjects immediately, and following a delay of 30 minutes. Likewise, Heaton et al. (1985), who examined 100 MS patients and 100 age and education matched controls, found a significant impairment of immediate verbal recall memory. Caine et al. (1986) reported impaired performance in their MS group, relative to matched controls, on an immediate story recall task. Fischer (1988) noted impaired immediate and 30 minute delayed recall memory in a group of 45 MS patients, compared with 25 sex, age, and education matched healthy controls. Franklin et al. (1988) also found impaired performance in a sample of 60 MS patients, relative to 60 demographically matched controls. They tested patients immediately after presentation, and following a 20 minute delay. Litvan et al. (1988b) reported MS patients as

exhibiting impaired verbal free recall memory, using immediate and 30 minute delayed assessments of a story. Immediate and delayed verbal free recall memory deficits in patients with MS were also recorded by Rao et al. (1989b). They compared their patient group with healthy controls, and found the patients were deficient on the immediate and one and 24 hour delayed assessments.

Minden et al. (1990), who assessed MS patients using immediate and 20 minute delayed recall trials, found the patient group significantly deficient, relative to the healthy controls. Rao et al. (1991a) also recorded impaired performance by MS patients on immediate, and one hour and 24 hour delayed recall trials, when compared with healthy controls. Goldstein et al. (1992) recorded 12 MS patients as performing significantly worse than 10 demographically matched controls, on both the immediate and 30 minute delayed assessments of a story recall task. Maurelli et al. (1992) noted deficient immediate verbal recall memory in their MS patients, when compared with matched controls. Swirsky-Sacchetti et al. (1992b) recorded 75% of MS patients as impaired on an immediate story recall task, and 50% as deficient on the 30 minute delayed trial. Likewise, Rao et al. (1993b) reported immediate and one hour delayed verbal free recall deficits in their patient group, relative to matched controls. Filippi et al. (1994) reported 12% of their MS patients as impaired on the immediate recall of a story. Grigsby et al. (1994) found impairment of immediate and 30 minute delayed story recall in a sample of 23 CP MS patients, relative to 23 age and education matched healthy controls. Comi et al. (1995), using established cut offs to define cognitive impairment, recorded 23% of their sample as impaired on a story recall test. Similarly, Kujala et al. (1996a) noted immediate and 60 minute delay verbal recall memory dysfunction in MS patients relative to matched healthy controls.

In contrast, Jennekens-Schinkel et al. (1990b) reported no significant differences between their MS patients and healthy controls on immediate or 30 minute delayed assessments of a story recall test. Likewise, Ruchkin et al. (1994), who assessed the performance of 10 MS patients, relative to that of 10 sex, age, and education matched healthy controls, on an immediate story recall task, found no significant difference between the two groups.

1.5.2 Visuo-Spatial Memory:

Visuo-spatial recall memory may be assessed using a variety of tasks which require the unprompted retrieval of items considered to be difficult to code verbally. The target stimuli tend to be real objects, designs, or patterns. Details of the actual tests used can be found in Sections 1.9 and 1.10.

Jambor (1969) found significant deficits of 10 minute delayed visuo-spatial recall memory in their MS patient sample, relative to both a healthy control group and patients with muscular dystrophy. Staples and Lincoln (1979) also reported deficiencies in learning and 10 minute delayed recall of visuo-spatial material, in the comparison with muscular dystrophy patients, but not in their large cohort of patients where impairment was derived from published norms. Grant et al. (1984) noted that their sample of MS patients demonstrated significant recall memory impairment, relative to age and education matched controls. They assessed patients immediately after presentation, and following a 45 minute delay. Rao et al. (1984) investigated visuo-spatial memory in CP MS patients, compared with age and education matched healthy controls, and patients with chronic pain. They recorded significant deficits in immediate and 30 minute delayed recall in the MS patient group, relative to both control samples.

Caine et al. (1986) reported a significant deficiency of immediate and 10 minute delayed visuo-spatial recall memory, when comparing MS patients with the controls. Beatty et al. (1988) investigated immediate visuo-spatial recall memory in a sample of CP MS patients. They found a significant impairment relative to matched controls, with 32% of the patient group performing below the fifth percentile. Likewise, Fischer (1988) recorded a significantly poorer performance by MS patients, than by matched controls, on both immediate and 30 minute delayed assessments of a visuo-spatial recall memory task. Franklin et al. (1988) noted that their MS patients were impaired on immediate visuo-spatial recall memory, but performed at a level not significantly different to that of the controls when assessed after a 20 minute delay.

Minden et al. (1990) reported immediate and 20 minute delayed visuo-spatial recall memory dysfunction in MS patients, relative to matched healthy controls. Pozzilli et al. (1991a) also noted a 15 minute delayed visuo-spatial recall memory deficit in their MS patients, when compared with healthy controls. Rao et al. (1991a) reported that 31% of their sample of MS patients were performing below the fifth percentile on a measure of visuo-spatial recall memory. Clark et al. (1992) reported impaired immediate recall memory in 123 MS patients, when compared with 60 matched controls. Swirsky-Sacchetti et al. (1992b) recorded 30% of patients as impaired on the immediate assessment of visuo-spatial recall memory, and 38% on the 30 minute delayed trial. Rao et al. (1993b) found the same result in their MS patients, again relative to demographically matched, healthy controls. Filippi et al. (1994) reported 19% of their MS patients as demonstrating deficient immediate visuo-spatial recall memory, while Beatty et al. (1995b) reported significant impairment of 30 minute delayed visuo-spatial recall in a large group of community based MS patients, relative to healthy controls. Likewise, Comi et al. (1995) recorded 29% of their patient group as impaired on an

immediate assessment of visuo-spatial recall memory. Kujala et al. (1996a) noted significant immediate and 30 minute delayed visuo-spatial recall memory deficits in their MS patients, when compared with matched, healthy controls. Ryan et al. (1996) found their sample of 177 MS patients were significantly impaired, relative to a group of 89 demographically matched, healthy controls. Furthermore, Rovaris et al. (1998) used established cut offs to demonstrate that 43% of their patient group were impaired on a visuo-spatial recall memory task. Camp et al. (1999) reported 13% of patients as impaired on the immediate assessment of visuo-spatial recall memory, and 14% on the 7 minute delayed trial, although the difference in scores between patients and controls did not reach statistical significance.

A small number of studies have reported no significant recent visuo-spatial recall memory impairment in MS patients relative to controls. Jennekens-Schinkel et al. (1990b) recorded no significant difference between the performance of patients and controls on either the immediate or 30 minute delayed assessments of a visuo-spatial recall task. Similarly, Maurelli et al. (1992) noted intact immediate visuo-spatial recall memory in patients with MS, as did Ruchkin et al. (1994).

1.5.3 Summary:

- The majority of group studies appear to suggest that immediate and delayed, recent recall memory for verbal stimuli, whether assessed with list learning tasks or story recall tests, is often impaired in patients with MS (Section 1.5.1).
- Likewise, there is much research to suggest that patients with MS can demonstrate significant dysfunction of recent visuo-spatial recall memory, at both immediate and delayed assessment (Section 1.5.2).

1.6 MEMORY FUNCTION IN MS: RECOGNITION MEMORY

Recognition memory may be described as an individual's ability to identify whether information or stimuli have been previously presented or are novel. Recognition memory tests support retrieval processes, as they provide items for direct yes/no judgements. Intact recognition memory set against a background of recall memory deficits, implies inadequate retrieval strategies, because the stimulus items are already available and do not need to be actively retrieved from the store. Impairment of all forms of memory function suggests additional difficulty in the encoding and storing of information, as the inability of prompts to aid retrieval indicate that information has not been encoded and processed initially. Recognition memory tests are often used in clinical practice as they appear useful in distinguishing neurological patients from those with depression (Coughlan & Hollows, 1984). However, normal performance on such an assessment does not necessarily indicate intact ability, as many recognition memory tasks have low ceiling levels (Rao et al., 1993b). Recent explicit recognition memory in MS has been examined in a variety of patient groups, using a range of neuropsychological tasks. This heterogeneity may contribute to the inconclusive findings in this memory domain. Details of the tests used can be found in Sections 1.9 and 1.10.

1.6.1 Verbal Memory:

Verbal recognition memory may be assessed by asking the subject to make judgements regarding whether items have been previously presented, or are unfamiliar. This type of task involves the presentation of a list of items. Recognition memory may also be examined by administering a series of multiple choice questions, following the

presentation of a story. As noted in verbal recall memory (Section 1.5.1), the recognition assessment following presentation of a story, does not provide as pure a measure of verbal recognition memory as that succeeding the presentation of a list of items, because the subject may reconstruct the story from schema.

1.6.1.1 List Learning Tasks:

Rao et al. (1984), in their study of CP MS patients, noted a significant deficit in immediate verbal recognition memory for words, relative to both patient and healthy control groups. Caine et al. (1986) also recorded their sample of MS patients as demonstrating significant deficits of 10 minute delayed verbal recognition memory, relative to demographically matched controls. Van den Burg et al. (1987) conducted a 25 minute delayed verbal recognition test for words. They found that recognition memory was significantly impaired in their sample of MS patients, relative to sex, age, and education matched controls. Beatty et al. (1988) assessed 30 minute delayed recognition memory for words, and demonstrated significant deficiencies in CP MS patients, relative to age and education matched controls. They noted that 42% of the patients performed below the fifth percentile. Minden et al. (1990) assessed 20 minute delayed recognition memory of a word list, and found significant impairments in their patient sample. Swirsky-Sacchetti et al. (1992b) reported 22% of their MS group as demonstrating deficiencies on a test of 20 minute delayed recognition memory.

Despite these results, which detail significant impairment of verbal recognition memory in patients with MS, the majority of researchers have noted that recognition memory is often less severely impaired than recall memory. However, some studies have found patients with MS to perform normally on verbal recognition memory tasks

for words. Carroll et al. (1984) reported intact verbal recognition memory in a sample of 22 MS patients and 22 sex, age, and education matched controls. Beatty et al. (1989) examined patients with RR MS using the same assessment of 30 minute delayed recognition memory as in their 1988 study. They reported no problems in their patient sample, compared to matched healthy controls. Rao et al. (1989b) using a one hour delayed recognition task for words, also found that the patient sample performed no differently to the matched control group. Jennekens-Schinkel et al. (1990b) reported intact immediate verbal recognition memory with visual presentation of the stimuli, but significant impairment when items were presented aurally. Ron et al. (1991), who assessed 58 patients with MS and 46 physically disabled controls, found no significant difference between the two groups on a test of immediate verbal recognition memory for words. Rao et al. (1993b) examined MS patients on a one hour delayed recognition memory test for words, and recorded that patients and matched controls performed similarly. Likewise, Armstrong et al. (1996) reported intact immediate verbal recognition memory in the MS patients, relative to the control group.

1.6.1.2 Story Recall Tasks:

Some researchers have assessed verbal recognition memory following the story recall task, by using a series of multiple choice questions. On a 30 minute delayed story recognition memory test, Beatty and Gange (1977) found a significant impairment in the performance of their MS patients, relative to that of sex, age, and education matched controls. Likewise, Caine et al. (1986) noted significant deficits of 10 minute delayed recognition memory of a story in their patient group, relative to matched controls. In

contrast, Minden et al. (1990) found no verbal recognition memory dysfunction when assessing 20 minute delayed recognition memory of a story.

1.6.2 Visuo-Spatial Memory:

Limited research has been conducted into visuo-spatial recognition memory in MS, but, as with verbal recognition memory, controversy remains as to whether this type of memory is dysfunctional in MS. Carroll et al. (1984) reported intact immediate visuo-spatial recognition memory in their MS patient group. In comparison, Fischer (1988) reported impaired immediate visuo-spatial recognition memory in MS patients, when compared with matched healthy controls. Ron et al. (1991) noted similar findings, when comparing MS patients with physically disabled controls.

1.6.3 Summary:

- There is conflicting evidence regarding dysfunction of both verbal and visuo-spatial recognition memory, using immediate and/or delayed assessments, in patients with MS (Sections 1.6.1 & 1.6.2).

1.7 MEMORY FUNCTION IN MS: PAIRED ASSOCIATION

Paired associate learning tests have been noted to be among the most sensitive measures for identifying memory impairment in neurological patient groups (Kapur, 1988). Wilson et al. (1985) report that this form of learning correlates highly with more naturalistic assessments of memory function, namely the Rivermead Behavioural Memory Test (Wilson et al., 1985; 1987a). Paired associate learning tests seem to be relatively sensitive indicators of the presence of memory impairment, which, according to Milner (1962), can be enhanced by including a delay component of 20 minutes or more. Paired association in MS has been assessed using a variety of tests and a heterogeneity of patient groups, both of which will inevitably impact on the findings. The tests used to examine paired association can be found in Sections 1.9 and 1.10.

1.7.1 Verbal Memory:

Verbal paired association tasks entail the presentation of pairs of words, and in the test phase, the subject is usually given the first item of a pair, and asked to recall the second. There are two types of verbal paired association stimuli: unrelated word pairs and semantically linked pairs. It has been suggested that the learning of word pairings which are unrelated, that is, low associate pairs, involves episodic memory alone (Wilson et al., 1982), although stimuli which are real words will inevitably evoke some activation in semantic memory. The learning of pairs which possess a meaningful association, high associate pairs, however, may make more use of semantic memory (Wilson et al., 1982). Tulving (1985) suggested that episodic memory is a relatively disorganised store, in which retrieval requires conscious searching. By comparison, semantic memory is highly structured, and may allow automatic access. Retrieval of

high associate pairings may, therefore, be facilitated, due to the efficiency of the search strategies which can be employed because of the structure of the system, and in extremis, the use of semantic skills to make an educated guess. Providing the distinct systems are acknowledged, the findings of Wilson et al. (1982) need not be problematic. However, in several studies, tests have been employed which comprise a mixture of high and low associate pairs, with the scores collated to give one, overall total. This practice may mask impairment, and provides limited information of the status of verbal paired associate memory. Further insights may be gained by the systematic separation of verbal paired association tasks into those using word pairs which have been engineered as either related or unrelated.

Jambor (1969) administered a form of paired associate learning to a sample of MS patients, a healthy control group, and patients with muscular dystrophy. He found that the MS sample were significantly impaired relative to these two control groups. Staples and Lincoln (1979) also demonstrated paired associate learning to be deficient in their MS group, relative to patients with muscular dystrophy. However, using published norms to assess the performance of the large MS cohort, patients were not classed as significantly deficient. Rao et al. (1984) noted that MS patients performed at a level no different to patient controls on immediate testing of paired associate learning. However, they noted that the MS patients recalled fewer words, relative to the controls, on the 30 minute delayed section of the same task. Huber et al. (1987) reported an impairment of immediate verbal paired associate memory in MS patients, relative to controls. Fischer (1988) recorded no impairment on immediate and 30 minute delayed assessment of semantically related word pairings, but significant dysfunction on both trials using low associate word pairs. Litvan et al. (1988b) also found that patients with MS

demonstrated a significant impairment in the number of word pairs immediately recalled, relative to that of the performance of the matched controls.

Jennekens-Schinkel et al. (1990b) compared the performance of MS patients with healthy controls, and found the patients significantly deficient on the immediate assessment of unrelated word pairings only. Minden et al. (1990) also reported a sample of MS patients performing significantly worse than matched controls on both immediate and 20 minute delayed assessments of a verbal paired association task, for both high and low associate pairs. Clark et al. (1992) reported patients as impaired on an immediate verbal paired association test, as did Maurelli et al. (1992), for both semantically linked and unrelated pairs. However, Filippi et al. (1994) found only 5% of the patient group demonstrated significant impairment on an immediate verbal paired association test. Amato et al. (1995) noted that patients with MS were significantly impaired, relative to matched controls on both the immediate and 10 minute and 24 hour delayed assessments. Comi et al. (1995) reported a low number of MS patients exhibiting deficits in immediate verbal paired associate memory (13%). Kujala et al. (1996a) recorded patients with MS to be impaired on both an immediate and 60 minute delayed paired association test. Ryan et al. (1996) also found deficits in their MS patients, relative to healthy controls.

1.7.2 Visuo-Spatial Memory:

There has been little investigation into visuo-spatial paired associate learning in MS. Beatty et al. (1988) assessed patients with a form of visuo-spatial paired associate memory, and found impairment in a sample of CP patients, relative to matched controls, on both the immediate and 30 minute delayed assessments. Beatty et al. (1989) reported

a similar deficit in RR patients, on an immediate paired association test. Fischer (1988), using a different visuo-spatial paired association test also found significantly poorer performance by patients, when compared with matched controls, on both immediate and 30 minute delayed trials. However, Ruchkin et al. (1994) recorded no significant difference in the performance of patients and healthy controls, on an immediate visuo-spatial task.

1.7.3 Summary:

- The research into paired associative memory is inconclusive, although many reports suggest an impaired performance, when using either verbal or visuo-spatial stimuli (Sections 1.7.1 & 1.7.2).

1.8 MEMORY FUNCTION MS: DEFICIT THEORIES

1.8.1 Retrieval Deficits:

The pattern of memory deficits found in patients with MS has been described by some researchers, for example, Rao (1986) and Rao et al. (1989b), as due to inadequate retrieval mechanisms, in the context of intact strategies for encoding and storage of information (Rao, 1986; Rao et al., 1989b). Evidence in favour of a retrieval deficit hypothesis comes predominantly from studies which show recognition memory to be unimpaired, or less affected, than recall memory in patients with MS. However, this may be premature, because recognition measures tend to have low ceiling levels, and, therefore, may mask any deficiencies (Rao et al., 1993b). Sensitivity to proactive interference is an alternative method for investigating the effects of encoding on secondary memory. Proactive interference occurs when new learning is disrupted by previously acquired information. As interference is dependent on similarity, it is possible to alleviate proactive interference by changing the nature of the target items after the first few trials. This is referred to as release from proactive interference or inhibition, and has been investigated by Beatty et al. (1989). They found that MS patients showed normal build up and release from proactive inhibition. Likewise, Rao et al. (1993b) reported no difference in the build up and release from proactive inhibition between the patient sample and the control group. These findings suggest that patients with MS encode semantic information normally. However, release from proactive inhibition does not provide any specific information about the encoding strategies employed by subjects. Intact semantic encoding in MS patients has been demonstrated using a variety of tasks (Carroll et al., 1984; Beatty & Monson, 1990; Rao et al., 1993b), which imply the structure of semantic memory remains unimpaired, and that the

memory deficits experienced by patients with MS may be due to difficulty in gaining access to lexical knowledge. The retrieval deficit hypothesis is further supported by Goldstein et al. (1992), who found MS patients to be as sensitive as controls to semantically related information, when administered a gist recall task (memory for important story ideas). In contrast, using a different semantic encoding task, Arnett et al. (1997) found deficiencies in MS patients, when compared with demographically matched controls. They suggested that the inability of MS patients to use categorical information effectively indicates a specific deficit in semantic encoding. These inconsistent findings may be reconciled by the suggestion that semantic encoding may only be disrupted if information processing demands are high (Carroll et al., 1984; Beatty et al., 1989).

Category fluency tasks may be considered to assess the ability to search semantic memory (Butters et al., 1985; 1986; Martin & Fedio, 1983). Further evidence in favour of the retrieval deficit hypothesis comes from studies which have demonstrated deficits on verbal fluency tasks in patients with MS. Beatty and Monson (1990) suggested that impairments in verbal fluency reflect difficulties in retrieving established verbal knowledge. In addition, Rao et al. (1989b) found deficiencies in verbal fluency to be correlated with deficits on list learning tasks, indicating problems with semantic retrieval. Normal learning and forgetting rates in MS patients are also thought to demonstrate that the memory problems exhibited by MS patients are due to failure of the retrieval mechanisms. However, studies which have compared learning and forgetting rates in MS patients with those of controls, usually give the patient group additional practice, in order that they can reach the performance level of the controls, hence the patients have rehearsed the items more frequently. The fact that MS patients demonstrate deficiencies in remote memory, which is equally severe for all decades, is

thought to imply equivalent loss of knowledge from both recent and distant past, again supporting the model of retrieval mechanism failure in MS. Armstrong et al. (1996) provided support for the retrieval deficit hypothesis in their investigation of the serial position and temporal cue effects in MS. They noted that patients demonstrated negative recency during spontaneous post-encoding retrieval, but normal recognition of the terminal words, and normal recency effects in the learning trials. They suggested that the items are placed in long-term storage during learning, but difficulties with the temporal order attributes of the word traces disrupt retrieval. Beatty and Monson (1991b) also found deficient temporal ordering in MS patients. However, Arnett et al. (1997) demonstrated intact ability, but considered the inconsistencies in the literature to be due to the variety of tasks employed. Grafman et al. (1991) found intact automatic processing in MS patients, and suggested that, as automatic processing relies on efficient encoding and storage of information, but, by definition, is independent of effortful retrieval, it would appear that the deficits in explicit memory may be explained by retrieval failure.

1.8.2 Encoding Deficits:

An alternative hypothesis suggests that aspects of encoding may be impaired, and, hence, responsible for the memory deficits exhibited by MS patients (Beatty, 1993). DeLuca et al. (1994) noted that several studies which compared MS patients with controls on list learning tasks have shown patients to demonstrate poor recall, but unaffected ability to learn. They commented that, given the reduced information initially acquired by the patients, subsequent recall deficiencies should be expected. DeLuca et al. (1994) reported MS patients requiring significantly more trials than controls to reach

a criterion on a verbal learning test, but once acquisition rate was controlled for, there was no significant difference in recall or recognition assessments between the two groups. DeLuca et al. (1994) suggested that the deficits in acquisition may be due to slow and inefficient information processing, and decreased storage and capacity of working memory. Van den Burg et al. (1987), Litvan et al. (1988b) and Jennikens-Schinkel et al. (1990b) also reported some of their patients exhibiting limited initial learning.

1.8.3 Heterogeneous Deficits:

Recent studies have noted the heterogeneity of memory dysfunction in patients with MS, which may indicate no single factor as responsible for the documented patterns of impairment (Fischer, 1988; Beatty, 1993; Beatty et al., 1996). Anatomically, initial encoding of information involves the diencephalic structures of the dorsomedial thalamic nuclei (Squire, 1982), the left prefrontal cortex, and the retrosplenial area (Shallice et al., 1994); whereas retrieval of information involves the medial temporal lobe structures of the hippocampus and amygdala (Squire, 1982), the right prefrontal cortex, and the bilateral precuneus (Shallice et al., 1994). All of these areas are affected by MS, although the subcortical regions are more prone to demyelination. Beatty et al. (1996) using the Selective Reminding Test (Buschke & Fuld, 1974) and cluster analysis, demonstrated that in a group of 99 MS patients, 25% performed normally, 22% showed deficits in encoding with inconsistent retrieval mechanisms, and 53% exhibited mild to moderate memory impairment. They emphasised that only two patients demonstrated a pure retrieval memory deficit. These data therefore imply that there is no uniform disturbance of memory in MS.

1.8.4 Summary:

- There is evidence which both supports and refutes the dichotomous models of encoding or retrieval deficits as the explanation of the memory deficiencies of patients with MS (Sections 1.8.1 & 1.8.2).
- As MS has a diffuse pathology, it is unlikely that a definitive theory will emerge which can explain the variety of different patterns of memory dysfunction exhibited by MS patients (Section 1.8.3).

1.9 TESTS OF MEMORY: CLINICAL ASSESSMENTS

A large variety of tests have been used to investigate memory function in patients with MS. A subset of these tasks have been published, and are routinely used in clinical cognitive assessments. These measures usually provide details of the standardisation and validation samples in which the test was developed, and often specify scaled scores and percentile equivalents of raw scores, which allows patient performance to be accurately gauged. The clinical memory assessments which have been most commonly used in studies of patients with MS are evaluated below.

1.9.1 Memory Batteries:

1.9.1.1 Wechsler Memory Scale (WMS): Wechsler (1945)

In 1987, Wechsler introduced a revised version of the WMS (Section 1.9.1.2). However, as numerous studies have used the original WMS or subtests from it to investigate memory function in MS, the measure is detailed below.

a) Content:

The WMS consists of a variety of subtests assessing different aspects of memory function. There are seven sections, namely, personal and current information, orientation, mental control, memory span, logical memory, visual reproduction, and associate learning. Personal and current information questions examine biographical data, both relevant to the individual, for example, "how old are you?", and of a more general nature, for example, "who is the president of the U.S.?". Orientation for time and place is assessed by asking the subject such questions as "what day of the month is it?". These two sections do not provide clear discrimination between normal and near

normal performance, and were included simply to identify specific deficits (e.g. aphasia & senility; Wechsler, 1945). The mental control subtest assesses overlearned material, for example, letters of the alphabet. Again, performance on this section is only of relevance for indicating specific defects (e.g. patients with organic brain disease; Wechsler, 1945). The memory span subtest is often referred to as the digit span task, and has already been detailed in Section 1.2.1.2.

The logical memory section involves recall of two brief stories. After presentation of each passage, the subject is asked to relate as many details as he or she can remember. Scoring criteria for the stories is imprecise (Lezak, 1995), allowing much subjectivity, and overall performance on this section is represented by the average of the number of correct ideas produced for both passages. This scoring procedure assumes equivalence in the levels of difficulty of the two stories. However, Ivison (1986), in a sample of 500 patients with no known memory impairments, reported that subjects systematically recalled more items from one of the passages, regardless of the order of presentation. A further shortcoming of this subtest is that attentional deficits may impede a subject's performance on the task. As the stories are presented aurally, the subject must maintain attention throughout, in order to attempt subsequent recall.

The visual reproduction subtest requires the subject to draw from memory three simple geometric designs, that are each exposed for 10 seconds. Again, scoring instructions are vague (Lezak, 1995). It has been argued that the visual stimuli comprising this section can be coded verbally, making the task not purely one of visuo-spatial recall (Lezak, 1995). Furthermore, the memory assessment may be an inaccurate reflection of ability in subjects with poor visual acuity and/or limited manual dexterity, whose compromised sensori-motor skills automatically place them at a disadvantage.

The associate learning section of the WMS involves 10 pairs of words, presented at the rate of one pair every two seconds. Six of the pairs are referred to as 'easy', with a semantic connection between the two items in a pair (e.g. "metal-iron"). The remaining four pairs are more difficult, as the words constituting a pair are unrelated (e.g. "cabbage-pen"). The subject is aurally presented with the word pairs, and in the test phase he or she is given the first item of a pair and asked to recall the second. There are three presentation-recall trials, and, if the subject responds correctly within five seconds of the stimulus word being presented, they are given a full credit for recalling hard associations, and half a credit for easy pairings. Paired associate learning tasks are considered to be relatively sensitive indicators of the presence of memory impairment (Kapur, 1988). However, Milner (1962) suggested that a delayed assessment may be more perceptive in identifying deficits. One of the disadvantages of this task is that it may appear abstract and artificial to the subject, who may fail to see the relevance of such an assessment to everyday life (Kapur, 1988). Another shortcoming of the WMS associate learning section is that memory performance on the high and low associate word pairs is collated, resulting in just one overall score of ability. As Wilson et al. (1982) reported that the learning of high and low associate word pairs places the emphasis on different memory systems (semantic & episodic, respectively), the amalgamation of the easy and hard pairing may mask deficiencies. The memory systems involved in high and low associate word pairs have been discussed in detail in Section 1.7.1. Patients with attentional dysfunction may also be placed at a disadvantage by the presentation format of this subtest, as the study phase entails reading aloud to the subject.

The scores on the individual subtests of the WMS can be converted to provide an overall memory quotient, corrected for age (Wechsler, 1945). A parallel form of the memory battery is also available (Stone et al., 1946), although, there is no standardisation of this form, and no formal comparison of the two versions (subjects were tested 1-16 days apart; Stone et al., 1946 simply noted that the differences between the mean scores of the forms were small).

b) Standardisation And Validation:

Normative data on the WMS comprised a sample of approximately 200 normal individuals (i.e. non hospital patients), with ages ranging from 20 to 50 years. Wechsler (1945) provided little information regarding the mental ability of the standardisation group, commenting that "In about 100 of these, intelligence ratings obtained with the Wechsler-Bellevue Adult Scale were also available". Comprehensive standardisation of the WMS using 237 subjects, and spanning the entire adult age range, from 15 to 89 years, was reported by Hulicka (1966). Ivison (1977) also calculated norms for the individual subtests of the WMS in a sample of 500 patients with no known memory impairments.

Modifications have been made to various subtests of the WMS, and these adapted version have been separately standardised and validated. Russell (1975) added a 30 minute delayed assessment to the logical memory and visual reproduction subtests of the WMS. Logue and Wyrick (1979; N=29), Brinkman et al. (1983; N=31), and Haaland et al. (1983; N=175) reported normative data on Russell's modified version of the WMS, whilst Logue and Wyrick (1979) also assessed 29 patients with dementia, and Brinkman et al. (1983) evaluated the performance of 25 patients with suspected Alzheimer's disease.

Hall and Toal (1957) administered the WMS to a sample of 150 patients with no psychosis, brain damage, or history of head trauma. They reported Cronbach's alpha of 0.81 for the logical memory subtest, 0.63 for the visual reproductions subtest, and 0.37 for the section assessing associate learning. The Cronbach's alpha for the total score was 0.70. Hall and Toal (1957) also evaluated the internal consistency of the WMS, and recorded intercorrelations between the various subtests, with coefficients ranging from 0.27 to 0.78. The total score on the WMS correlated significantly with the full scale score on the Wechsler-Bellevue Intelligence Scale (Wechsler, 1946; $r = 0.75$), and Hall and Toal (1957) suggested that there was considerable overlap between the cognitive domains assessed by these two measures. Factor analyses of the WMS have revealed a variety of solutions (Erickson & Scott, 1977).

c) Comments:

The WMS has the advantage of brevity in administration, taking approximately 15 minutes to complete. In addition, the calculation of a memory quotient provides an overall estimate of memory ability. However, coincident with the shortcomings of each individual subtest, the restricted age range of the original standardisation sample is an obvious weakness of the battery (Erickson & Scott, 1977). The data terminate at an age when the greatest changes in normal memory function begin to occur, and where the incidence of central nervous system abnormalities increases (Lezak, 1995). The WMS has been further criticised for the inclusion of unnecessary, non memory items such as reciting the alphabet (Kapur, 1988), and for the bias towards verbal memory, with only one subtest assessing memory for visual stimuli (Kapur, 1988; Lezak, 1995). Rao and Bieliauskas (1983) also reported the scale to be relatively insensitive to some forms of right hemisphere pathology, suggesting support for the notion that the memory quotient may reflect predominantly verbal memory function.

The WMS places emphasis purely on the measurement of immediate and short-term memory capabilities, with no assessment of long-term memory skills (Kapur, 1988). In addition, the single summary score, thought to reflect overall memory capability, does not accommodate the differentiation of separate memory functions (Lezak, 1995). The calculation of the memory quotient also assumes that each subtest of the WMS contributes equally in an additive fashion (i.e. it is assumed that memory is a unidimensional function), with the various subtests corrected only for age (Lezak, 1995).

Hall and Toal (1957) commented that the values of the intercorrelation coefficients for the subtests of the WMS were mixed, and in some cases so low that the range of scores between impaired and intact patients would not differentiate between the two groups. Cohen (1950) reported that the WMS failed to differentiate among a heterogeneous patient group, comprising psychoneurotics (N=81), organics (N=45), and schizophrenics (N=18). Howard (1950; 1953) also demonstrated the poor diagnostic value of the WMS. In addition, Prigatano (1977) noted that the WMS discriminated poorly between impaired and intact patients. The patient group comprised 31 patients with known brain dysfunction, and 26 patients with unconfirmed brain dysfunction.

1.9.1.2 Wechsler Memory Scale-Revised (WMS-R): Wechsler (1987)

a) Content:

The WMS-R revises and expands the original scale in an attempt to examine a wider range of memory functions and address some of the criticisms levelled at the original battery of tasks. The modified version includes the following subtests; information and orientation questions, mental control, figural memory, logical memory

I, visual paired associates I, verbal paired associates I, visual reproduction I, digit span, visual memory span, logical memory II, visual paired associates II, verbal paired associates II, and visual reproduction II. The information and orientation questions, mental control, and digit span tasks remain relatively unchanged from the original version. The visual memory span subtest is a visual-spatial analogue of the digit span section, in which the subject observes the examiner, touching a series of coloured squares in a predetermined order, at the rate of one per second. He or she must then replicate that order. The number of squares touched increases after two trials, if either is recalled correctly. The task is then repeated with the subject being required to touch the squares in the reverse order to that in which they were demonstrated. This subtest may prove difficult for patients with poor visual acuity and/or limited manual dexterity, in whom considerable processing may be engaged in the physical requirements of the task.

The figural memory subtest involves showing the subject an abstract design for five seconds, and then asking him or her to select that item from a choice of three figures. The subsequent three trials involve presentation of three abstract designs in the study phase, displayed for a total of 15 seconds, and then requiring the subject to identify those previously seen from a choice of nine items. This task demands good visual acuity as the abstract designs have fine detail. In addition, the test may be criticised for not being a pure visuo-spatial memory assessment, because the items can be coded verbally.

Logical memory I follows a similar format to that of the original WMS, although the second paragraph has been replaced by one more equivalent in difficulty to that of the first passage. Logical memory II simply requires subjects to recall the stories a second time, after a delay of 30 minutes. The scoring criteria have been made more specific and exhaustive in order to increase objectivity in these sections, and the total

score represents the complete number of ideas recalled in both paragraphs. Patients with attentional deficits may still be automatically penalised on the subtest, because listening to the stories as they are read, is a fundamental, initial stage of memory.

The visual reproduction I section comprises four simple geometric designs, each being shown to the subject for 10 seconds. After presentation of each item, he or she is asked to draw the figure from memory. A 30 minute delayed assessment has also been included, which is referred to as visual reproduction II. The scoring system for these sections has been improved which reduces inter scorer variability. However, the problems of poor sensori-motor skills artificially biasing performance for patients, such as those with MS, remains an issue, limiting the usefulness of the task for assessing memory function in such a population. In addition, the stimuli are still relatively easy to code verbally, and therefore do not represent a pure test of visual memory (Lezak, 1995; Wilson, 1996).

The verbal paired associates I subtest of the WMS-R attempts to overcome some of the problems of the original associate learning section. The test involves eight pairs of words, four pairs of 'easy' associations and an equal number of 'hard' pairings. The pairs are presented at the rate of one every three seconds, and there are a maximum of six trials, in which the subject must attempt to learn the pairs to yield one perfect repetition. Only the first three trials are scored, and after an interval of 30 minutes, the subject is again asked to recall the second item of each pair (verbal paired associates II). All items are scored equally. The issue of high and low associations placing emphasis on different memory systems (Wilson et al., 1982), hence suggesting the usefulness of separate scores for the two types of pairings, has not been considered, nor has the additional difficulty placed on individuals with attentional deficits.

The stimuli for the visual paired associates sections comprise six abstract line drawings, each paired with a different colour. In the visual paired associates I subtest, the subject is shown each of these pairs for three seconds and after presentation of all six cards, he or she is given each figure and asked to identify, from a colour chart, that with which it was associated in the original presentation. There are a maximum of six presentation-recall trials in order to reach the criterion of one perfect repetition, however, only the first three trials are scored. Visual paired associates II entails the repeat of the test phase after an interval of 30 minutes. These subtests of the WMS may be inappropriate for patients with poor manual dexterity and/or visual acuity, as such skills are necessary to carry out the physical requirements of the task. In addition, it is apparent that colours have names and therefore can act as verbal cues, making the subtests an inaccurate measure of visual paired associate learning. Wechsler (1987) attempts to overcome this problem by stating in the manual "in order to minimise the role of verbal mediation in memorising and responding to the figure-colour pairs, the colour names are not used either in presenting the items or responding to them". However, this seems to be a weak and ineffective attempt to avoid the use of verbal labels.

Scores on the individual subtests of the WMS-R can be collated. The single global summary score of the WMS (the memory quotient), has been replaced with five composite scores, namely; general memory, attention/concentration, verbal memory, visual memory, and delayed recall.

b) Standardisation And Validation:

The WMS-R has been standardised in a sample of 450 subjects, with ages ranging from 16 to 74 years. However, for certain age groups, namely 18 to 19 years, 25 to 34 years, and 45 to 54 years, the data have been extrapolated, assuming cognitive

performance declines linearly with age. Percentiles are available for the digit span, visual memory span, logical memory I and II, and visual reproduction I and II, subtests of the WMS-R. The scale has been validated using a sample of 341 patients with a variety of conditions (including 29 MS patients). The patient groups demonstrated characteristic memory impairments using the WMS-R (Wechsler, 1987).

Wechsler (1987) reported that the average reliability coefficients across age groups for the subtests of the WMS-R and the composite scores ranged from 0.41 to 0.90 (median value 0.74). The intercorrelations between the indices ranged from 0.13 to 0.92 (Wechsler, 1987). Factor analysis of the standardisation sample data revealed a two factor solution, with a general memory and learning factor, and an attention/ concentration component. The factor analysis of the clinical sample revealed a similar pattern of factor loadings. In the standardisation sample, sex was not reported to have a significant influence on test scores, whilst the significant effects of ageing and education on WMS-R performance were demonstrated (Wechsler, 1987).

Delis et al. (1988) reported strong correlations between the WMS-R and the California Verbal Learning Test (CVLT; Section 1.9.2.3). The correlation coefficient between the delayed memory index of the WMS-R and the CVLT long-term delayed free recall score was 0.93. Butters et al. (1988b) reported that the WMS-R differentiated between amnesic and demented patients, and Janowsky et al. (1989) recorded differences in the impairment patterns of Korsakoff patients (N=7), and patients with frontal lobe lesions (N=7).

c) Comments:

The revised version of the WMS has addressed a number of the criticisms of the original scale, although several shortfalls persist. Supplementary to the problems associated with each subtest, there are weaknesses in the overall structure of the

memory measure. The five indices of the WMS-R are useful, however, Bornstein and Chelune (1988) reported that in a factor analysis study of 434 patients with a variety of diagnoses, the separate quotients, and/or the contributing tests were not discriminated. In addition, the intercorrelations between different subtest of the WMS-R range in value, with intercorrelations between measures grouped within the same summary score often demonstrating low coefficients, suggesting that different functions are being assessed (Lezak, 1995).

The WMS-R has relatively low ceiling levels for several subtests, which Wechsler (1987) justifies by reporting it to be a scale principally designed to detect poor memory function. Wechsler (1987) also comments that the scale is not suitable for making fine discriminations at high levels of memory functioning. The ceiling effects, and poor sensitivity of some sections are disappointing features of the WMS-R.

Many investigators have used sections of the WMS or WMS-R, both with and without variations, in order to assess memory function in patients with MS (Young et al., 1976; Staples & Lincoln, 1979; Grant et al., 1984; Rao et al., 1984; Heaton et al., 1985; Rao et al., 1985, Lyon-Caen et al., 1986; Huber et al., 1987; Brainin et al., 1988; Fischer, 1988; Franklin et al., 1988; Litvan et al., 1988a; 1988b; Jennekens-Schinkel et al., 1990b; Minden et al., 1990; Klonoff et al., 1991; Goldstein et al., 1992; Huber et al., 1992; Kessler et al., 1992; Maurelli et al., 1992; Swirsky-Sacchetti et al., 1992b; Comi et al., 1993; Mattioli et al., 1993; Grigsby et al., 1994; Ruchkin et al., 1994; Basso et al., 1996; Kujala et al., 1996a; Ryan et al., 1996; Kujala et al., 1997; Van Buchem et al., 1998).

1.9.1.3 Recognition Memory Tests (For Words, RMTW; And For Faces, RMTF): Warrington (1984)

a) Content:

Ron et al. (1991) and Rozewicz et al. (1996) used the RMTW and RMTF to assess memory function in patients with MS. The RMTW is an immediate forced-choice recognition memory test of 50 words. The target items are drawn from a pool of 4 to 6 letter words, each of which possess an A or AA frequency (Thorndike & Lorge, 1944). The words are printed on individual cards, and in the study phase, they are presented to the subject at the rate of one every three seconds. During this time, he or she is asked to judge whether the item evokes pleasant or unpleasant associations, responding "yes" or "no" respectively. Recognition memory is assessed immediately after presentation of the items, using a word card consisting of 50 pairs of words. Each pair comprises a target item and a distractor. The distractors words are taken from the same pool as the targets (noted above). In the test phase, the subject is required to read aloud or point to those words he or she considers to have been previously seen. The subject is encouraged to choose one item from each pair. The order of the stimulus list is not maintained for the recognition task, and the position of target items within each pair is randomised.

The RMTF follows a similar format to that detailed above. The target stimuli comprise 50 photographs of unknown males. These are presented to the subject at the rate of one every three seconds. For each photograph, the subject is asked to respond "yes" if the man looks pleasant, or "no" if he is not so pleasant. On completion of the study phase, the subject is then presented with 50 pairs of photographs. In each case one is a target item, the other a distractor. The distractor stimuli are taken from the same category as the target stimuli, and for each pair, the subject must point to the item which

he or she has seen before. The order of the stimulus list is not maintained, and the left/right position of the items is randomised.

b) Standardisation And Validation:

The RMTW and RMTF have been standardised using a sample of 310 volunteers with ages ranging from 18 to 70 years. The sample was considered to represent a cross section of the adult population of the area, consisting of in-patients with extracerebral disease at various London hospitals, their relations, and friends. Using the standardisation sample, the intercorrelation coefficient between the RMTW and the RMTF was 0.36 ($p<0.001$). Performance on the RMTW correlated significantly, in a negative direction with age ($r = -0.35$, $p<0.001$), and significantly, in a positive direction, with two measures of general intelligence, namely, the Mill Hill Vocabulary (Raven, 1965; $r = 0.38$, $p<0.001$), and the Advanced Progressive Matrices (Raven, 1962; $r = 0.45$, $p<0.001$). Similarly, performance on the RMTF correlated significantly, in a negative direction with age ($r = -0.13$, $p<0.05$), and positively with the Mill Hill Vocabulary ($r = 0.26$, $p<0.001$), and the Advanced Progressive Matrices ($r = 0.33$, $p<0.001$). As the RMTW and RMTF demonstrated age effects, the sample was subdivided into three age groups: 18-39 years, 40-54 years, and 55-70 years. Using these three categories, percentile scores and normalised scores were derived. Warrington (1984) reported that the test scores of the RMTW were skewed towards a ceiling level in the younger age group of the standardisation sample. However, she noted that in a clinically useful memory test the severity of deficits, rather than the degree of excellence, was of relevance.

Validation of the RMTW and the RMTF was achieved by studying the performance of patients with lateralised cerebral lesions (145 patients with left hemisphere lesions, and 134 patients with right hemisphere lesions). Analyses of their

performance demonstrated that the RMTW and the RMTF detected material specific memory deficits. One hundred and twelve patients with proven cerebral atrophy were also studied as a validation sample of patients with diffuse brain disease. Individuals were only included in the sample if clinical consideration saw adequate language and perceptual skills, sufficient for task demands. Hence the selection procedure eliminated all patients with an obviously dementing condition. It was noted that even patients with minor degrees of atrophy were impaired on the RMTW and the RMTF, demonstrating the sensitivity of the measure.

Compton et al. (1992) conducted a factor analysis of the RMTW and RMTF with Russell's modified version of the Wechsler Memory Scale (Wechsler, 1945; Russell, 1975). They noted that the two test batteries measured relatively independent aspects of memory function. Squire and Shimamura (1986) used the RMTW and the RMTF to assess verbal and nonverbal recognition memory function in 10 amnesic patients (6 Korsakoff's patients and 4 amnesic cases with other aetiologies). They reported that both measures graded ability, and demonstrated the potential to discriminate among the different patient groups. In addition, Diesfeldt (1990) reported that their patient group performed more poorly than healthy controls on the RMTW and the RMTF. They examined 44 patients with dementia of the Alzheimer type, and 45 non demented, elderly subjects. They also recorded a intercorrelation coefficient between the verbal and nonverbal version (i.e. RMTW and RMTF) of 0.40 ($p<0.01$), in the patient group, and 0.29, in the age matched controls, indicating that the two tests do not assess exactly the same concept. Hermann et al. (1995) and Kneebone et al. (1997) reported that both tasks were sensitive to lateralised temporal lobe lesions, although they did not identify laterality preoperatively. Bigler et al. (1996) also noted that in patients with

moderate to severe traumatic head injury (N=83), performance on the RMTW and the RMTF did not relate to hippocampal atrophy assessed using MRI.

c) Comments:

Squire and Shimamura (1986) commented on the ease of administration and scoring of the RMTW and the RMTF. The tasks have also been noted to provide a relatively pure measure of memory, because the study and test procedures place few demands on physical capabilities and/or other cognitive skills (Langdon, 1996). Another advantage of the RMTW and the RMTF, as with other recognition memory assessments, is that they are less vulnerable to the effects of anxiety and depression (Coughlan & Hollows, 1984). In addition, the matched format of the RMTW and the RMTF allows the comparison of memory across modalities, and hence permits the accurate comparison of the contributions of the left and right hemispheres.

Despite the advantages noted above, Squire and Shimamura (1986) criticised the initial instructions for subjects, which are read at the onset of the study phase. They commented that the objective of the tasks, as tests of memory is not emphasised, and the focus is placed on the decision making process. Squire and Shimamura (1986) also suggested that a 24 hour delayed assessment may be a more perceptive indicator of deficiencies than immediate testing. Reliability data have not been reported for either the RMTW or the RMTF. In addition, Lees and Smith (1983) failed to find a significant recognition memory impairment in their PD patients (N=30), implying that the measure may lack sensitivity.

Despite the option to point to or read aloud the stimulus items in the test phase of the RMTW, which has been noted as an advantage of the test, permitting administration to patients with speech difficulties, patients with poor visual acuity have not been accommodated. They may be able to read the single words presented during

the study phase, but may be unable to study the word card in the test phase. To assess memory, these items would need to be read to the subject, changing the modality between encoding and retrieval, which may compromise performance. The difficulties for patients with visual disturbances are accentuated in the RMTF, where the photographs require good visual acuity in order to discriminate individual features.

The RMTF has been criticised by Kapur (1988), who noted that in the validation sample, overall group mean scores of patients with left hemisphere lesions, as well as those with right hemisphere lesions, were impaired relative to controls. This suggests that, in contrast to that outlined by Warrington (1984), the face recognition task may not be highly specific to right hemisphere pathology. An alternate explanation for this finding, is that the nonverbal stimuli comprise the torso of the male, not just his face, hence verbal cues (e.g. jacket, tie etc.) may have been used to aid memory (Kapur, 1988). Although distractor stimuli are of a similar composition, patients often use verbal cues, creating an assessment with a verbal element. Yin (1970) supported this suggestion, reporting that if verbal cues are minimised, focal memory deficits may be readily detected. Finally, as face recognition may utilise different memory processes to those employed in tasks using other types of nonverbal stimuli, comparisons between performance on the RMTF and other visuo-spatial memory assessments may be inappropriate.

1.9.2 Verbal Memory Tests:

1.9.2.1 Babcock Sentence Learning Test: Babcock (1930)

a) Content:

The Babcock Sentence Learning Test was used by Jambor (1969), to examine verbal recall memory in patients with MS. This is a recall memory assessment, comprising a single sentence ("One thing a nation must have to become rich and great is a large, secure supply of wood"), which is used to examine supraspran memory. The subject must attempt to recall the sentence, and he or she is given six trials in which to do so.

b) Standardisation, Validation, And Comments:

Little detailed standardisation has been recorded for this test, and Warburton (1963) reported that healthy, elderly individuals (N=80) failed the task, suggesting restricted usefulness in a clinical setting (Kopelman, 1986). Kopelman (1986) also demonstrated that performance on the Babcock Sentence Learning Test did not discriminate between various patient groups and healthy controls (16 Alzheimer's disease patients; 16 Korsakoff patients; 16 depressed patients; 16 controls). In addition, the Babcock Sentence Learning Test automatically handicaps subjects with attentional deficits, due to the mode of presentation. Attention must be maintained throughout the study phase, as this is an essential staging post to memory.

1.9.2.2 Rey Auditory Verbal Learning Test (RAVLT): Rey (1964)

a) Content:

The stimuli for this test consist of 15 unrelated common nouns, which are read aloud to the subject at the rate of one per second. There are five presentation-recall trials of the first list. A second list, again of 15 words, is then presented and recall of these items assessed. Following this, recall of the first list is retested. Free recall of the initial list after 30 minutes may also be assessed, followed by a recognition memory test. The recognition assessment entailed the subject indicating as many words as possible from the initial list when shown, or read, a list of 50 items. These items were words from either of the lists previously presented, or words semantically related or phonemically similar to the target items. An alternative recognition memory assessment was provided by Rosenberg et al. (1984), who presented the subject with a story, from which they were required to identify words from the original list. This test succeeded the recall memory assessment of the initial word list following the interference condition. Minden et al. (1990) also adapted the RAVLT. They shortened the word list by removing the last five items from each set, assessed immediate recognition using the notion of words embedded in a story, and included a 20 minute delayed free recall and recognition assessment of the initial list. The delayed recognition assessment entailed identifying the original words from a list of target and distractor items. Crawford et al. (1989) developed parallel forms of the word lists.

b) Standardisation And Validation:

Rey (1964) provided norms for subjects aged between 15 and 90 years on trials one to five of the RAVLT. Query and Megran (1983) have also published detailed normative data based on 677 subjects, with ages ranging from 19 to 81 years. A shortfall

of their data is that it may not be truly representative of a healthy adult population because their sample consisted of male inpatients, who had not suffered severe brain damage. Query and Megan (1983) did not indicate whether subjects with mild or moderate degrees of cerebral pathology were also excluded. Bleecker et al. (1988) provided normative data based on a sample of 196 healthy controls, aged 40 to 89 years, and Selnes et al. (1991) assessed 733 healthy male individuals. Age effects are prominent on the RAVLT (Bleecker et al., 1988; Selnes et al., 1991). Sex has also been found to significantly impact on performance (Bleecker et al., 1988), as has education (Bleecker et al., 1988; Selnes et al., 1991).

In a factor analysis of the scores of 146 healthy individuals, Vakil and Blachstein (1993) identified a three factor solution. The factors comprised a short-term memory component, a storage component, and a retrieval component. Crossen and Weins (1994) also reported that the RAVLT correlated moderately well with the California Verbal Learning Test (detailed in Section 1.9.2.3).

Janowsky et al. (1989) reported that patients with frontal lobe lesions (N=7) performed consistently below that of healthy controls on the RAVLT. Similarly, Leininger et al. (1990) reported that the RAVLT differentiated between 53 symptomatic minor head injury patients and 23 uninjured healthy controls. The RAVLT has also been shown to be useful in delineating memory deficits associated with a variety of disorders. Rosenberg et al. (1984) provided validation of the RAVLT in a sample of 92 psychiatric and neurological patients, divided according to those with and without memory impairments. The RAVLT discriminated well between the two groups. Butters et al. (1985; 1986) noted that the RAVLT differentiated the patterns of memory dysfunction in patients with Huntington's disease and Alzheimer's disease. Squire and Shimamura (1986) also reported that the RAVLT discriminated effectively between different types

of amnesic patients and healthy controls (6 Korsakoff patients, 4 other amnesic patients, 8 healthy controls). Bigler et al. (1989), in a sample of 94 patients with dementia of the Alzheimer's type or closed head injury, reported the measure to differentiate the distinct memory defects of the two samples. Ivnik et al. (1988), also found the test to discriminate between patients with left (N=64) and right (N=78) temporal lobe lesions. There were slight differences between the scores of the two group preoperatively and marked discrepancies following anterior temporal lobectomy.

c) Comments:

The RAVLT appears to offer a comprehensive assessment of verbal learning and memory, however, when completing the recognition task of words incorporated into a story, Query and Megran (1983) recorded ceiling levels in their younger subjects, suggesting that this particular section may not detect minor degrees of memory impairment. In addition, the modifications to the test, added by various researchers have not necessarily been standardised or validated. The task also requires attention to be maintained throughout the presentation phases of the assessment, which may automatically handicap patients with attentional dysfunction.

Verbal learning, recall, and recognition have been investigated in MS patients using the RAVLT and its modified versions by Medaer et al. (1987), Litvan et al. (1988b), Minden et al. (1990), Caltagirone et al. (1991), Pozzilli et al. (1991a), Maurelli et al. (1992), Armstrong et al. (1996), D'Esposito et al. (1996), and Van Buchem et al. (1998).

1.9.2.3 California Verbal Learning Test (CVLT): Delis et al. (1987)

a) Content:

The CVLT was introduced to expand the format of the RAVLT. It comprises a 16 item shopping list, with stimuli taken from four semantic categories. Words are presented aurally to the subject at the rate of one every second, with five immediate presentation-recall trials. Short delay free and cued recall are assessed following the presentation and free recall of a distractor list. After a 20 minute interval, long delay free and cued recall are examined. Delayed recognition memory is also assessed by asking the subject to identify, from a list of 44 items, those in the original shopping list. The 28 distractors of the recognition assessment originate from distinct groups; they may be from the same semantic categories as the first list, but are actually found in the interference list, they may be from the distractor list but unrelated to items from list one, they may be prototypical items from the categories of the original shopping list, they may be items phonemically similar to those of the initial list, or they may be unrelated shopping items.

The CVLT word list has been constructed so that it includes both high frequency, well established categories, for example clothing, and lower frequency 'fuzzy' (Rosch, 1975) categories, for example spices and herbs. This is to minimise floor effects in brain damaged populations, and ceiling effects in normals. The word frequencies of items within each category are also varied systematically for the same reason. The test allows a multifactorial assessment of verbal learning and memory, detailing the strategies used to recall and recognise information at the various time points. There is also a parallel form of this test (Delis et al., 1991).

b) Standardisation And Validation:

Normative data have been collected on a sample of 273 neurologically intact individuals, with an age range of 17 to 80 years (Delis et al., 1987). It is also possible to convert raw scores into standard scores. Performance on the CVLT correlates highly with age (Delis et al., 1987), and moderately with level of education (Delis et al., 1991). Kramer et al. (1988) also reported a significant correlation between sex and recall performance, with women demonstrating superior ability (N=136 neurologically intact individuals). In the control sample the Cronbach's alpha for trials 1-5 was 0.69, and 0.86 in a mixed sample of clinical and non-clinical subjects (Delis et al., 1987).

Factor analysis of the CVLT in 286 healthy controls, and 113 neurological patients revealed similar solutions. Six factors were identified, namely, a general learning factor, learning strategy, acquisition rate, serial position effect, discriminability, and learning interference (Delis et al., 1987). These factors are reported to correspond to empirical findings in theoretical studies of memory (Delis et al., 1987).

The CVLT has been validated in a sample of 145 patients with a variety of neurological disorders, of which 56 were classified as MS patients. The test has also been shown to correlate moderately with the WMS (Delis et al., 1988). The CVLT has been reported to discriminate patients from healthy controls. Crosson et al. (1988) compared the performance of 33 head injured patients and 33 healthy controls, detailing three different patterns of deficits in the patient group (problems with consolidation, encoding, or retrieval). Hermann et al. (1987) also reported that the CVLT differentiated ability between patients with left (N=15) and right (N=15) temporal lobe seizures, and healthy controls (N=15). The patterns of deficits on the CVLT, in patients with various neurological conditions have been detailed (Delis et al., 1987), and the test appears to discriminate between different conditions. Massman et al. (1992) reported that

performance on the CVLT produced different patterns of deficits in Alzheimer's disease patients (N=20), Huntington's disease patients (N=20), and healthy controls (N=40).

c) Comments:

The CVLT is a comprehensive test of verbal learning and memory, with a structure which allows the determination of how errors are made, and therefore has the potential to identify the strategies, processes, and errors associated with specific deficits. Despite this, it has been criticised, as the scores cannot be evaluated in terms of learning ability alone, nor can they provide unequivocal dissociation between functions because of the possible contributions of conceptual apprehension or organisation (Lezak, 1995). In addition, the CVLT, as its name suggests, is Californian, and the vocabulary is slightly different to that used in England. This creates difficulties for the English patient, because items such as sweater and slacks are unfamiliar, and may be encoded as jumper and trousers, which are scored as incorrect, despite their more natural, semantic sense. The test is also very long and perhaps attempts to measure too many aspects of verbal memory function. Likewise, the scoring is protracted and lengthy. The CVLT may prove problematic for patients who exhibit impaired attention, as this must be maintained throughout the presentation of the list to enable memory to be assessed. One of the problems with the recognition memory assessment of the CVLT is that it follows the free and cued delayed recall trials. There is therefore a very long interval between the original presentation of the items and the recognition memory task. However, Milner (1962) noted that delayed assessments are often more sensitive measures of recognition memory than immediate recognition trials.

The CVLT has been used by Kessler et al. (1992), and Swirsky-Sacchetti et al. (1992b) to examine verbal recall and recognition memory in MS patients.

1.9.2.4 Selective Reminding Test (SRT): Buschke and Fuld (1974)

a) Content:

This test entails learning a list of words which are presented aurally at the rate of one item every two seconds. The whole list is presented on the first trial, and on all subsequent trials the subject is reminded only of the words that were missed on the preceding trial. He or she must, however, attempt to recall the entire list on each recall assessment. In their original test, Buschke and Fuld (1974) used 10 animal names as the stimuli, which the subject had to recall over 15 trials. The scoring criteria suggested by Buschke and Fuld (1974) allows the division of items into those stored in what is termed 'long term retrieval' and 'consistent long term retention', and this permits detailed analysis of recall performance and the separation of various aspects of storage and retrieval (Buschke,1973). Hannay and Levin (1985) introduced a modified version of the SRT involving 12 unrelated words learnt over a series of 12 consecutive recall trials. They also proposed a one hour delayed recall assessment and recognition memory test. The task to investigate recognition memory involved the subject discriminating the initial 12 words which were mixed with 12 distractor items. A recent version of the SRT entails 6 immediate recall trials of the 12 item list, followed by a delayed recall assessment after approximately 15 minutes (Rao et al., 1990). DeLuca et al. (1994) also modified the SRT by using the original version of this task, but including 30 minute delayed recall and recognition conditions.

b) Standardisation And Validation:

Buschke and Fuld (1974) illustrated the usefulness of their test by recording the performance of a 55 year old lady with chronic alcoholism. Normative data has been collected by Ruff et al. (1988), who assessed 392 healthy individuals, stratified by sex, age, and education, Larrabee et al. (1988), who assessed 271 healthy individuals aged

18 to 91 years, and Masur et al. (1989), who examined a sample of 134 healthy elderly subjects. Age and sex have been found to correlate with performance on the SRT (Ruff et al., 1988). The influence of education on performance, however, is less pronounced (Ruff et al., 1988; Larrabee et al., 1988). Intercorrelations between the variables of the SRT have been reported as strong (Loring & Papanicolaou, 1987), suggesting that they are measuring similar, or the same functions.

Macartney-Filgate and Vrizen (1988) reported modest correlations between the SRT and other tests of verbal learning and memory (the WMS, & RAVLT). The SRT has been shown to distinguish well between patients and healthy controls. Levin et al. (1979) reported the SRT to discriminate between patients with severe head injury and healthy controls. In addition, Masur et al. (1989) examined 134 healthy elderly subjects, and 21 patients with Alzheimer's disease. They reported that the patients performed significantly below the controls on the SRT. Masur et al. (1990) went on to note that the SRT appeared useful as a preclinical indicator of the development of dementia. Paniak et al. (1989) also assessed 21 patients with severe closed head injury and matched hospitalised controls with no history of head trauma, neurological disease, or psychiatric illness, and noted that the patients performed significantly below the control group.

The SRT has been reported to discriminate between a variety of patient groups. Lee et al. (1989) noted that the SRT differentiated between patients with right and left temporal lobe lesions. Stern et al. (1992) recorded patients with dementia alone, or combined with Parkinson's disease or stroke, scored significantly below those of non-demented Parkinson's or stroke patients. In addition, Levin et al. (1979) reported that the severity of closed head injury was related to memory performance on the SRT.

c) Comments:

The SRT has the advantage that it differentiates the relative contributions of retention, storage, and retrieval. However, the use of items from the same category in the original form of the test has been criticised by Erickson and Scott (1977) and Lezak (1995), as it allows guesswork to be employed. The subject may simply select items from a given category without definite recollection of a specific name (Lezak, 1995). Another weakness of the test, and the modified versions, lies in the use of only 10 or 12 stimulus items, which may not be sufficiently challenging for individuals with superior memory capabilities. This task may be difficult for patients with attentional deficits, as the stimuli are read aloud, thus attention must remain focused throughout each presentation of the items, in order to allow accurate measurement of memory.

The basic structure of the test has been used by Rao et al. (1989a; 1991; 1993b), DeLuca et al. (1994), Beatty et al. (1995b; 1995c; 1996), Hohol et al. (1997), Rovaris et al. (1998), and Camp et al. (1999) to assess verbal memory in patients with MS.

1.9.2.5 Five Items and Paired Words Subtests of the Randt Memory Battery: Randt et al. (1980), Randt and Brown (1986)

a) Content:

The Five Items and Paired Words subtests of the Randt Memory Battery were used to assess verbal memory in a sample of MS patients by Amato et al. (1995). The Five Items subtest entails the learning and long-term retention of five, monosyllabic words, which are presented aurally. The words are all AA or A frequency nouns (Thorndike & Lorge, 1944), with high and concrete imagery. After the first presentation-recall trial, the subject is only reminded of the items missed and recall of

all words is retested. There are a maximum of three presentation-recall trials. Re-assessment is not required if the subject recalls all the items correctly. Recall memory is also assessed after three minutes, and again after 24 hours. In both of the delayed assessments, recall memory is examined before the three (or fewer) presentation-recall trials are administered.

The Paired Words subtest involves six paired association items; two pairs are words which can be logically combined (e.g. "ear/ring"), two items have a strong internal association between the words of a pair (e.g. " dream/sleep"), and two pairs comprise unrelated items. The restricted reminding technique is employed, such that the subject is only reminded of the items missed overall, not just on the preceding trial. Recall is tested immediately and following delays of three minutes and 24 hours. The restricted reminding technique is adopted independently for each of these assessments.

b) Standardisation And Validation:

Randt et al. (1980) and Randt and Brown (1986) have reported normative data for 200 healthy subjects with ages ranging from 20 to 79 years. They also demonstrated that performance on the five items and paired words subtests declined with age. Similarly, Osborne et al. (1982) recorded moderate sensitivity to age effects. Fioravanti et al. (1985) and Franzen et al. (1989) have provided additional standardisation for the battery.

Randt et al. (1980) validated the five items and paired words subtests of the Randt Memory Battery in a group of 24 individuals, although these were poorly defined (characterised by the features of over 60 years of age, with memory loss and cognitive impairment, but lacking focal neurological deficits; there is no distinction of aetiology in the patient group). Five parallel forms of the memory scale are available.

c) Comments:

The Randt Memory Battery has been criticised for its emphasis on verbal memory (Lezak, 1995). Erickson and Howieson (1986) also suggested that the five items and paired word subtests of the Randt Memory Battery, may be too easy to discriminate the memory capabilities of young patients with mild memory deficits, who may still be at ceiling level on the tasks. In addition, the aural presentation of the stimuli in the five items and paired words subtests of the Randt Memory Battery may automatically penalise patients with attentional deficits.

1.9.2.6 Memory Subscale of the California Short Form Test of Mental Maturity Level 5 (CSFTMM): Sullivan et al. (1963)

a) Content:

This is a measure of verbal recognition memory, in which the subject is presented aurally with a short story, and following a delay of approximately 35 minutes, required to answer 25, four alternative multiple choice questions.

b) Standardisation, Validation, And Comments:

The CSFTMM is a standardised intelligence test, which was frequently used during the 1960s and 1970s in public schools. It has seven subtests in total, which on factor analysis by the Thurstone centroid method indicate four main emphases; logical reasoning, numerical reasoning, verbal concepts, and memory. Level 5 is the most advanced form. Despite being used by Beatty and Gange (1977) to assess memory function in patients with MS, the memory subscale of the CSFTMM has not been validated for use in clinical populations.

Details of the content of the story, are not provided, not are there any administration guidelines. In addition, it is unclear whether the multiple choice questions are presented aurally or are written for the subject to study. The modality of the study and test phases may handicap some patients: subjects with attentional dysfunction may find the aural presentation of the story difficult, whilst those with visual disturbances may be placed at a disadvantage if the test questions are presented visually. Interpretation of the paragraph may also affect responses to the multiple choice questions, and schema may be used to respond to questions where the subject is unsure of the correct response. Currently, the multiple choice format is not frequently used in clinical practice, and it is not directly comparable to a forced choice recognition memory test.

1.9.2.7 The Modified Word Learning Test: Walton and Black (1957), Walton et al. (1959)

a) Content:

This is a type of paired association task used by Jambor (1969) to assess verbal memory function in patients with MS. The assessment comprises eight unfamiliar nouns, verbally presented to the subject, in order that he or she may learn their meaning. The stimulus items are fribble, kermes, gibus, vervaine, stanhope, gaby, burin, and rebeck, and they are presented in the same order for five trials. Recall is tested after each presentation.

b) Standardisation, Validation, And Comments:

Data have been collected on the Modified Word Learning Test using a sample of 57 healthy controls and 222 psychiatric patients (125 neurotics, 30 psychotics, 21

mental defectives, & 46 brain damaged patients). Walton and Black (1957) reported that age and intelligence did not affect the scores significantly, and there was little overlap between organic and inorganic patients. They also noted that the task appeared capable of differentiating organic patients with cortical damage, from functionals, and healthy controls. Walton et al. (1959) confirmed the task's validity in a group of 83 controls and 221 patients (66 neurotics, 32 psychotics, 45 mental defectives, & 78 organics). In addition, Walton (1958) and Inglis (1959) demonstrated that the test had predictive validity and prognostic value in patients over 65 years. Newcombe and Steinberg (1964) recorded no significant relationship between performance on the Modified Walton-Black Test and age or intelligence. They did not find a significant difference between the performance of matched functional (N=13) and organic (N=9) patients. The test may be also be criticised for its lack of applicability for patients with attentional dysfunction, who may be automatically penalised by the verbal presentation of the target stimuli.

1.9.3 Visuo-Spatial Memory Tests:

1.9.3.1 Complex Figure Test (Rey-Osterrieth Figure): Rey (1941), Osterrieth (1944)

a) Content:

This is a test of visuo-spatial recall memory in which the subject is required to copy a complex figure, and then reproduce it from memory. In the original version (Rey, 1941) recall was assessed after three minutes. However, there are a number of modified versions of this task in which the time point(s) of the recall assessment(s) are varied (Spreen & Strauss, 1991). There are also numerous scoring criteria (Spreen & Strauss, 1991).

b) Standardisation And Validation:

Consideration of the method of administration and the scoring criteria must be made when using normative data. The variation in these factors has led to a large number of published standardisation samples. Using a sample of 60 adults, aged between 16 and 60 years, Osterrieth (1944) provided limited normative data for the copying, and three minute recall trials of the task.

The internal consistency of the Complex Figure task has been evaluated by treating each detail as a separate item, and using Cronbach's alpha. Berry et al. (1991) reported a value of 0.60 for the copy condition, and 0.80 for recall, suggesting that all the details of the task measure a single factor. Meyers and Meyers (1995) assessed 601 healthy controls, and reported intercorrelations of the immediate recall (3 minutes) and delayed recall assessments of $r = 0.88$. Moderate correlations were also recorded between copying and immediate recall ($r = 0.33$), and copying and delayed recall ($r = 0.38$), suggesting that there is a relationship between ability to copy the figure and memory performance.

Performance on the Complex Figure task has been reported to correlate significantly, in a negative direction with age, and in a positive direction with intelligence (Boone et al., 1993). There is conflicting evidence regarding the influence of gender on memory performance using this task. Berry et al. (1991) and Boone et al. (1993; 91 healthy individuals) reported no significant relationship between the two variables, whilst Bennet-Levy (1984), in a sample of 107 healthy controls, reported that males demonstrated superior performance.

Meyers and Meyers (1995) conducted a factor analysis on the data from the standardisation sample. They reported a five factor solution, namely, visuo-spatial recall, visuo-spatial recognition, response bias, processing speed, and visuo-spatial

construction ability. Their analysis of 100 brain damaged patients revealed the same solution. Berry et al. (1991) also conducted a factor analysis, and reported a visuo-spatial/memory factor. Meyers and Meyers (1995) examined the relationship between performance on the Complex Figure task, and that of other conventional memory assessments. In a sample of patients with various neurological disorders, copying, immediate recall, and delayed recall correlated significantly with total score on the Benton Visual Retention Test, and trial 5 of the RAVLT.

The Complex figure task has been used to assess visuo-spatial memory function in a variety of patient groups. Brooks (1972) reported severe memory deficits in a sample of 27 patients with closed head injuries, when compared with 16 age and education matched orthopaedic outpatients. The test has been shown to discriminate patients with probable Alzheimer's disease from healthy controls (Berry et al., 1991), and Leininger et al. (1990) reported the task to be sensitive in patients with minor head injury (53 patients assessed 1-22 months following concussion and mild concussion, & 23 demographically matched healthy controls). Bigler et al. (1989) noted that in their sample of 94 patients with Alzheimer's disease and closed head injury, the Alzheimer's disease patients exhibited greater difficulty in both copying and recall. Furthermore, Bigler et al. (1996) also reported that the degree of hippocampal atrophy in moderate to severe head injury patients was related to recall performance on this test.

c) Comments:

There are a large number of different versions of the Complex Figure, which employ various administration and scoring procedures. Caution must be taken when identifying norms for the task. One of the major shortfalls of administering this task to a patient sample is that individuals with compromised sensori-motor skills may be automatically penalised because efficient manual dexterity and good visual acuity are

prerequisites. Patients with poor visuo-spatial and/or planning or organisation skills may also be disadvantaged by the test (Wilson, 1996), as these additional cognitive functions are necessary to complete the task. In addition, the figure and/or its constituents can be coded verbally (Wilson, 1996), therefore the assessment may not be a true test of visuo-spatial memory capability. Kapur (1988) commented on the inaccuracies of recall tasks which initially require the subject to copy the stimuli. He suggested that subsequent recall capability may be imprecisely measured, because of the individual differences in reproduction which are acquired during copying. These may impact on the subject's retention of the stimuli, and hence distort recall. Loring et al. (1990) suggested that a delayed assessment may be more sensitive to the presence of various memory deficits.

Franklin et al. (1988), Pozzilli et al., 1991a, Fontaine et al. (1994), D'Esposito et al. (1996), and Van Buchem et al. (1998) used the Rey-Osterrieth Figure to assess visuo-spatial recall memory in patients with MS.

1.9.3.2 7/24 Spatial Recall Test (7/24 SRT): Barbizet and Cany (1968)

a) Content:

This task involves seven chips randomly positioned on a 6 x 4 grid. After a 10 second study period, the subject is provided with nine chips and an empty grid and asked to reproduce the design. This presentation-recall format is repeated for a total of 15 trials, or until the subject has learnt the pattern. The subject is retested after delays of five minutes, 30 minutes, and 24 hours.

Rao et al. (1984) modified the 7/24 SRT by using only five immediate presentation-recall trials, followed by the presentation of a second design and free recall examination of that pattern. The subject was then asked to reproduce the original array

again. After an interval of 30 minutes, recall of the initial design was retested. Another variation of the 7/24 SRT was introduced by Rao (1990), and was referred to as the 10/36 spatial recall test. The stimuli for this task were 10 chips, placed on a 6 x 6 grid. The subject was given 10 seconds in which to study the array and was then asked to reproduce it. There were three immediate presentation-recall trials and a delayed assessment after approximately 15 minutes.

b) Standardisation, Validation, And Comments:

Data on the original 7/24 SRT has been collected on normal controls between the ages of 41 and 79 years, but there is little clinical data available. There is also sparse standardisation and validation of the modified versions of the task. Rao et al. (1984; 1985; 1989a), Jennekens-Schinkel et al. (1990b), Rao et al. (1991; 1993b), Kujala et al. (1996a), Hohol et al. (1997), Kujala et al. (1997), Rovaris et al. (1998), and Camp et al. (1999) have all used the 7/24 SRT or the modified versions to assess patients with MS. Many of the studies collected data from healthy controls, however, these control samples were matched to the patient groups.

Rao et al. (1984) commented that their form of the 7/24 SRT should be amenable to patients with MS, as the display is large and placement of the chips does not require fine motor co-ordination. However, Langdon (personal communication) has noted that patients find positioning the counters difficult, often using a lot of processing simply to undertake the physical requirements of the task. Rao et al. (1984) reported that MS patients with severe ataxia may direct the examiner in placing the counters, although this encourages verbal coding of the target positions as co-ordinates, implying that the test may not be a pure measure of visuo-spatial memory (Lezak, 1995). Lezak (1995) also reported that the 7/24 SRT has a relatively low ceiling level, limiting the sensitivity of the test in distinguishing different memory capabilities.

1.9.3.3 Benton Visual Retention Test (BVRT): Benton (1946)

a) Content:

The BVRT is a test of visual recall memory comprising a series of 10 figures, which are studied by the subject and then must be drawn from memory. There are three different forms of administration; five or 10 seconds exposure to the design followed by immediate recall, or a 10 second study period, followed by a 15 second delay, and then the recall assessment. There are both quantitative and qualitative methods of scoring the reproductions, and there are four parallel forms of the BVRT. Two multiple choice forms are also available for patients with poor manual dexterity, however, these assess visuo-spatial recognition, rather than recall memory.

b) Standardisation And Validation:

As there are several version of the BVRT (the fifth edition of the test was published in 1992; Benton-Sivan, 1992), there is much data regarding the standardisation and validation of the measure. Benton et al. (1974) reported normative data on the BVRT, and demonstrated strong age effects, and a high correlation between performance on the test and intelligence ($r = 0.70$). Arenberg (1978) also collected data on a large standardisation sample (N=857). Youngjohn et al. (1993) provided additional normative data on the BVRT, administering the test to 1128 healthy individuals, with an age range of 17 years to over 70 years. They found a significant negative association between age and performance on the BVRT, a positive relationship between BVRT performance and level of education, but no relationship with sex. Steck et al. (1990) reported the Cronbach's alpha of the delayed recall assessment version of the BVRT as 0.79.

The BVRT appears to be sensitive to memory impairments in a variety of patient groups. Heaton et al. (1978) assessed psychiatric patients and patients with organic brain disease, and reported the BVRT to discriminate well between the two groups. Eslinger et al. (1985) also demonstrated that the BVRT differentiated dementia from normal ageing. Botwinick et al. (1986) administered the BVRT to a sample of 18 patients with mild dementia of the Alzheimer type, and 30 matched healthy controls. They recorded a significant difference in the performance of the two groups over a four year period. Similarly, Storandt et al. (1986), who conducted a longitudinal study of 43 patients with mild Alzheimer's disease, and 43 matched healthy controls, reported the BVRT to discriminate well between the two groups over time. Levin et al. (1990) also reported that the test discriminated between patients with severe head injury and matched controls, whilst Youngjohn et al. (1992) noted that the BVRT differentiated between patients with Alzheimer's disease (N=56) and age, sex, and education matched controls (N=56).

c) Comments:

The BVRT has the advantages of brevity in administration time, precise scoring criteria, and many alternate forms. A variety of different types of errors can also be identified, namely: omission, distortions, perseverations, rotations, misplacements, and size errors. However, the stimulus items are easy to code verbally (Lezak, 1995), and, therefore, do not represent a pure test of visuo-spatial memory. In addition, Larrabee et al. (1985), who assessed the factor structure of the BVRT (N=102 patients of mixed aetiology), reported that the test loaded primarily on a visual/perceptual/motor factor, and secondarily on memory, and attention/concentration. This indicates that the BVRT predominantly assesses visuo-construction skills, rather than memory.

The BVRT has been used by Medaer et al. (1987), Clark et al. (1992), Kujala et al. (1996b), Ryan et al. (1996), and Kujala et al. (1997) to assess visuo-spatial recall memory function in MS patients.

1.9.4 Summary:

- There are a variety of published tests which have been employed to assess verbal and visuo-spatial memory function in patients with MS. It must be noted, however, that none of the memory tests reviewed assess all the memory domains of verbal and visuo-spatial recall memory, paired association, and recognition memory. In addition, the tasks often possess various shortfalls, which suggest that they may be inappropriate for the assessment of memory in MS.
- Table 1.9.1 summarises for each test whether it is deemed appropriate for the evaluation of memory in patients with MS, and whether it does, does not, or it is unclear whether it gives rise to impaired performance in previous MS samples.

Table 1.9.1: A Summary Of The Appropriateness Of Each Test Detailed, And Previous Findings In MS Samples

CLINICAL MEMORY ASSESMENTS	Approp.	Prev. Impaired	Prev. Intact	Prev. Unclear
1.9.1.1 WMS: logical memory	~	✓		
visual reproductions	×	✓		
paired associates	~			✓
1.9.1.2 WMS-R: logical memory	~	✓		
verb. paired associates	~			✓
visual reproductions	×	✓		
vis. paired associates	×			✓
figural memory	~	✓		
1.9.1.3 RMT	~			✓
1.9.2.1 Babcock Sentences	~			✓
1.9.2.2 RAVLT	~	✓		
1.9.2.3 CVLT	~	✓		
1.9.2.4 SRT	~	✓		
1.9.2.5 Five Items	~			✓
Paired Words	~	✓		
1.9.2.6 CSFTMM	~	✓		
1.9.2.7 Modified Word Learning	~	✓		
1.9.3.1 Complex Figure	×	✓		
1.9.3.2 7/24 SRT	×	✓		
1.9.3.3 BVRT	×	✓		

Appropriateness: ~ reasonably appropriate with some reservations (see relevant section); × not appropriate

1.10 TESTS OF MEMORY: RESEARCH ASSESSMENTS

The materials and test administration procedures of the clinical tasks detailed in Section 1.9 are readily available to the neuropsychologist, and despite the shortfalls noted above, the majority of measures report at least small standardisation and validation studies. However, much research into memory function in MS has been conducted without utilising published, clinical memory assessments. Research tests are typically designed to examine a specific memory function in a given patient group, with little attention to the psychometric properties of the newly developed measure. The tasks are usually administered exclusively to the research sample, with no information regarding the appropriateness, reliability, validity, or sensitivity of the assessment tool. Results based on such tests must be treated with caution, as the robustness and coherence of the actual measure are unknown, and therefore their impact on the recorded patient scores cannot be quantified. The use of research assessments, administered to only one group of subjects, also prevents the detailed comparison of results across studies.

1.10.1 Verbal Memory Tests:

Several researchers have investigated verbal memory function in patients with MS by using their own word list or story recall assessments. Beatty and Gange (1977) assessed 26 MS patients and 26 sex, age, and education matched healthy controls, using their own list learning task. The word list comprised 24 items, each of which possessed values greater than 5.00 on norms of imagery, concreteness, and meaningfulness (Paivio et al., 1968), and appeared 20 or more times out of a million words (Kucera & Francis, 1967). Homonyms were excluded. The stimuli were presented aurally to the subject at

two second intervals, and after presentation of the last item a bell was rung, and the subject was required to recall as many words as possible. There were four trials, each involving the 24 words presented in a different order. The subject was encouraged to repeat words from the end of the list first. This instruction was taken from Watkins and Watkins (1974), and aimed to promote the reproduction of items from short-term memory before they were lost.

Rao et al. (1984; 1985; 1989b) also employed their own verbal free recall test. In their 1984 study, 44 MS patients, 23 chronic pain patients, and 15 age and education matched healthy controls were assessed; in their 1985 study, 47 MS patients were assessed; and in their 1989b study, Rao et al. assessed 37 MS patients and 26 healthy controls matched for age, education, and verbal intelligence. The stimuli comprised 12 nouns of 10 letters or less, taken from the norms of Paivio et al. (1968). All items had a frequency usage count greater than one (Kucera & Francis, 1967), and Christian et al. (1978) norms were used to equate the words for frequency and ease of free recall. The list was read to the subject with a two second pause between items. Free recall was then assessed. There were a total of five presentation-recall trials, after which a second list of 12 nouns, with the same criteria for selection as the initial list, was read to the subject. Following recall of these items, the subject was again required to recall items from the initial list. Recognition memory of the original stimuli was then assessed, and delayed free recall was examined after 30 minutes. The recognition memory task required the subject to select the original 12 items from a list in which they were mixed with 12 novel words. Three alternate forms of the test were administered in the 1984 and 1985 studies, and no significant differences between the test forms were reported. In their 1989b study, Rao et al. adopted the scoring criteria of Tulving and Colotla (1970), to aid the separation of the relative contributions of primary and secondary memory. If the

number of word presentations and recall productions intervening between presentation and recall of a word was seven or less, the word was assigned to primary memory. All other items were considered to originate from secondary memory.

Caine et al. (1986) used their own verbal free recall task to assess 30 MS patients, 21 HD patients, and 15 healthy controls, matched for age and education. The test was developed as part of the Boston/Rochester Neuropsychological Screening Test (Kaplan & Caine, 1981, unpublished). It involved the learning of 10 words over five trials, followed by 10 minute delayed free recall and recognition assessments. No administrative details for the recognition test are provided in the 1986 paper. Caine et al. (1986) also used a story recall task, again devised as part of the Boston/Rochester Neuropsychological Screening Test (Kaplan & Caine, 1981, unpublished). In this task, the subject was required to recall a story which he or she had read twice; once silently, and once aloud. After the immediate free recall test, multiple choice questions were presented. Rao et al. (1989b; 1991; 1993b) administered this test to their MS patients There were 37 MS patients and 26 age, education, and verbal intelligence matched healthy controls in their 1989b study; 100 MS patients and 100 demographically matched healthy controls in the 1991 study; and the 1993b study assessed 46 MS patients and 47 demographically matched healthy controls. Rao et al. (1989b; 1991; 1993b) did not use the multiple choice section of the task. Instead, they assessed delayed recall at intervals of one hour and 24 hours. Unpublished data for 300 patients and 100 controls of various ages have been collected on the word list, and story recall tasks (Kaplan & Caine 1981, unpublished). However, the data were used to reformulate the test items, in order to enhance the reliability and validity of the measure.

Another multitrial free recall test was developed by Van den Burg et al. (1987). The subject was presented aurally with a list of 15 words at the rate of one every two

seconds. There were five immediate presentation-recall trials, and free recall and recognition memory were also examined after a 25 minute delay. The recognition assessment required the subject to indicate the 15 target items from a written sheet of 30 words. The 15 targets and the 15 distractor stimuli were randomly interchanged. Van den Burg et al. (1987) used the measure to assess verbal memory function in 40 MS patients, compared with that of 40 sex, age, and education matched healthy controls. They also collected normative data on a sample of 168 healthy subjects, and reported test-retest reliability coefficients of 0.80 and 0.85, for learning and delayed recall respectively, with an interval of two to three months (Van Den Burg et al., 1987).

Beatty et al. (1988; 1989) devised a 14 item verbal recall test. The stimuli comprised seven high and seven low imagery words. These were read to the subject at the rate of one word every two seconds. After presentation, the subject immediately attempted to recall as many words as possible in any order. The list was then repeated in a different order. There was a total of four presentation-recall trials, followed by delayed (30 minutes) recall and recognition memory assessments. The verbal recognition task comprised 28 words; the 14 target items and 14 distractors. The subject was required to indicate the items he or she considered had been previously presented. Beatty et al. (1988) assessed 38 MS patients and 26 age and education matched healthy controls, whilst in their 1989 study they examined 42 MS patients, compared with 24 sex, age, and education matched healthy controls.

Jennekens-Schinkel et al. (1990b) devised their own verbal memory task, assessing the impact of visual and aural presentation of the stimuli on recall ability. They used 10 nouns per list, which were matched exactly for frequency (Van Berckel et al., 1965), and for the distribution of mono and bi syllables. Plurals were excluded. For the visual presentation condition, the word list included five items from the category

"occupations", interspersed with five random words. Stimuli were presented at the rate of one word per second. In the aural presentation condition, the targets comprised five words from the category "animals", again mixed with five random words, and the 10 items were presented in 17 seconds. In both conditions there were five presentation-recall trials, and recall was assessed by asking the subject to respond orally. Delayed recall was examined after 30 minutes for the aural presentation section, and following a 60 minute delay for the visual presentation condition. Recognition memory was tested using a yes-no procedure. The lists used in the recognition assessment comprised five distractors from the relevant category of the target list, and 25 random items. Jennekens-Schinkel et al. (1990b) used this task to assess 39 MS patients and 24 healthy controls matched for socio-economic status.

Kujala et al. (1996a; 1997) designed a verbal list learning task in which the subject was read a set of 10 words from the category fruits/vegetables. Following recall of as many items as possible, the subject was informed of the words missed, and recall tested again, with the instruction to begin with those omitted on the previous trial. There were six trials using this format. The subject was then given another list of 10 words from the same category, and asked to recall them. Following the interference condition, memory of the initial list was retested. Kujala et al. (1996a) assessed 45 MS patients and 35 healthy controls using this test, and followed-up 42 of the patients and 34 of the controls (Kujala et al., 1997).

Carroll et al. (1984) devised a recognition memory test for words, in which the items comprised five related nouns, taken from nine semantic categories. The categories were musical instruments, prints, drinks, vegetables, metals, birds, weapons, animals, and professions. There was also one group of nine unrelated words. All nouns possessed frequencies between 10 and 40 occurrences per million (Thorndike & Lorge, 1944). In

the study phase of this task, three words from each of the nine semantic categories were selected. These were individually presented on cards to the subject, in a random order, at the rate of one every five seconds. The subject was instructed to use whatever strategy may help them to recognise the items on a subsequent occasion. In the test phase, the 27 target words were presented with an equal number of novel items. The remaining words of the pool were used as the distractors. The subject was required to identify the items previously studied. Carroll et al. (1984) used this test to assess verbal memory in 22 patients with MS, and 22 sex, age, and education matched healthy controls.

Heaton et al. (1985), Filley et al. (1989), Anzola et al. (1990), Mariani et al. (1991), Filippi et al. (1994), and Comi et al. (1995), have also used their own verbal memory tests to examine recall, recognition, and paired associate learning capabilities in patients with MS. The main shortfall of all these tasks is their limited standardisation and validation. In addition, instructions of test procedure are often unavailable, which are vital to ensure uniformity of test administration and scoring. Changes in modality between presentation and testing (e.g. presenting a subject aurally with the stimuli, but asking him or her to identify previously seen items by reading through a word list), may also have an adverse effect on the accurate measurement of memory skills. The subject may find certain modalities easier than others; patients with attentional deficits may find the aural presentation of stimuli more difficult, whilst individuals with poor visual acuity may be placed at an unfair disadvantage when a visual test modality is employed.

In word list tasks, details of item selection, frequency of usage, and/or semantic category are often lacking. That the items are taken from published frequency charts, and have been carefully selected, does not imply a reliable and valid test. Story recall tasks possess the inherent problem of constructing the paragraphs along precise parameters (Kapur, 1988). Furthermore, Kapur (1988) has suggested that a delayed

story recall assessment may offer a more sensitive measure of memory function, than immediate testing. A shortfall of paired associate learning tasks is that they may seem unusual, difficult, and possibly inappropriate to the subject, who may fail to see the relevance of the task to everyday life (Kapur, 1988).

1.10.2 Visuo-Spatial Memory Tests:

A number of researchers have investigated visuo-spatial memory function using their own assessments. The pictorial test of delayed recall was introduced by Jambor (1969), and comprised nine pictures presented on a card to the subject. The items were moon, bird, bicycle, book, can, drum, boots, cockerel, and teapot. The subject was asked to try and memorise the stimuli, being allowed to look at the pictures for as long as was necessary to name all the items twice in sequence. Instructions for the administration of the test are limited. In addition, although the pictures are visuo-spatial stimuli, they are readily identifiable by name, making them easy to code verbally. This coding is also encouraged, by asking the subject to name the items, not draw them, or select the items from an array. Jambor et al. (1969) used this task to assess 75 MS patients and 79 healthy controls.

Caine et al. (1986) also devised a visuo-spatial memory test in which the subject was required to recall visually presented figures. Following an immediate recall test, the items were copied, and recall was reassessed after a 10 minute delay. In the 1986 paper there are no details of the type of figures used, the mode of presentation, the length of exposure to the items, the modality of the recall assessment, or the scoring criteria. Patients with poor visual acuity and/or manual dexterity may be penalised by the format of the test. In addition, a task which requires copying inherently allows individual

differences in the reproductions, which may contribute to enhancing or compromising memory performance (Kapur, 1988). If the subject does not copy a figure accurately, the correct form has not been encoded, and therefore cannot be retrieved precisely. Data from 300 patients and 100 controls of varying ages have been collected by Kaplan and Caine (1981, unpublished) on this task. However, following the analyses, small adjustments were made to enhance the test.

Beatty and Troster (1987), and Beatty et al. (1988) developed a visuo-spatial recall task, referred to as the New Map Test. It was introduced as an anterograde equivalent of the Fargo Map Test (Beatty, 1988). Using an outline map of three fictitious states, on which 15 imaginary cities were marked, the subject was instructed to study the location of the cities. After 60 seconds, he or she was given a blank map with 25 numbered dots. At the top of the sheet were the names of the cities, and the subject was required to identify the proper location of each city by writing its identification number next to the name on the answer sheet, or by linking the two orally. When the subject had located as many cities as possible, the target map was presented for a further 60 seconds. There were a total of four presentation-recall trials. One of the drawbacks of the NMT is that performance may be biased by an individual's general spatial ability, highlighting the need for detailed standardisation. In addition, patients with poor manual dexterity and/or visual acuity may find the physical requirements of the task difficult, automatically placing them at a disadvantage. The NMT may also be criticised for failing to satisfying the criteria of a visuo-spatial assessment. As the cities have been named, they may be coded with a mnemonic, acting as a verbal reference. The NMT was used by Beatty et al. (1988; 1995b) to examine visuo-spatial recall memory in patients with MS.

Beatty et al. (1988) also introduced an additional section to the Symbol Digit Modalities Test (SDMT; Smith, 1973), succeeding standard administration of the test (Smith, 1973). On completion of the 90 second substitution phase, the subject was required to study the symbol digit key for 30 seconds and attempt to memorise it. Recall of the key was then immediately assessed, and retested after a 30 minute delay. No further administration details are provided. One of the main problems of this adaptation of the SDMT is controlling for the level of recall already acquired, before the 30 second study phase. Individuals process information at different speeds, therefore details acquired during the substitution phase cannot be accurately gauged. In addition, the task does not assess pure visuo-spatial memory, as the symbols are verbally codeable (e.g. cross, moon, etc.), and these are paired with numbers. Another shortcoming of the test is the automatic handicap for patients with limited visual acuity, who may be unfairly disadvantaged by the format of the task. This additional section of the SDMT was used by Beatty et al. (1988; 1989) to examine recall ability in MS patients.

Carroll et al. (1984) developed a visuo-spatial recognition memory test, which involved 80 standardised line drawings, selected for their high picture-name agreement, from a pool created by Snodgrass and Vanderwart (1980). In the study phase 40 slides were used, and the subject was required to complete either a shallow or deep orientation task. In the test phase, the 40 target items were shown with the remaining 40 unseen slides. The subject was asked to respond "yes" to those previously seen, and "no" to unfamiliar slides. Patients with poor visual acuity may be placed at a disadvantage on this task. In addition, the problem of measuring pure visuo-spatial memory arises, as all the items were chosen for their high picture-name agreement, hence they can be coded verbally.

Anzola et al. (1990), Mariani et al. (1993), Filippi et al. (1994), and Comi et al. (1995), used the Corsi supraspan test, a variation of the Corsi span test (Milner, 1971), in which the sequence to be remembered may exceed the subject's span of apprehension. In contrast, Kujala et al. (1996a) and Ryan et al. (1996) devised their own object recall memory task. All researchers provide sparse details of the stimuli or administration procedures. The unpublished visuo-spatial memory assessments specified above have limited use, even if comparisons have been made with matched controls. Standardisation is unavailable because the pattern of function of the healthy individuals is unlikely to span the normal range of ability, and the reliability of the assessments remains unquantified. In addition, if validation of the task has not been conducted, the sensitivity and specificity of the test remain unknown. Coincident with the shortfalls of the individual measures, recurring problems have been noted when administering these tasks to patients with compromised manual dexterity and/or visual acuity, who are automatically disadvantaged by their limited sensori-motor skills.

1.10.3 Summary:

- There are a variety of unpublished, research tests which have been employed to assess verbal and visuo-spatial memory functions in patients with MS. Again, it must be noted that none of the memory tests reviewed assess all the memory domains of verbal and visuo-spatial recall memory, paired association, and recognition memory. The research assessments also possess a variety of shortfalls, which may imply that the tests are not appropriate for the evaluation of memory in patients with MS.

- Table 1.10.1 summarises for each test, whether it is deemed appropriate for the assessment of memory in patients with MS, and whether it does, does not, or it is unclear whether it gives rise to impaired performance in previous MS samples.

Table 1.10.1: A Summary Of The Appropriateness Of Each Test Detailed, And Previous Findings In MS Samples

RESEARCH MEMORY ASSESMENTS	Approp.	Prev. Impaired	Prev. Intact	Prev. Unclear
1.10.1 Beatty & Gange (1977)	~	✓		
1.10.1 Rao et al. (1984)	~	✓		
1.10.1 Caine et al. (1986)	~	✓		
1.10.1 Van Den Burg et al. (1987)	~	✓		
1.10.1 Beatty et al. (1988)	~	✓		
1.10.1 Jennekens-Schinkel et al. (1990)	~			✓
1.10.1 Kujala et al. (1996a)	~	✓		
1.10.1 Carroll et al. (1984)	~		✓	
1.10.2 Jambor (1969)	×	✓		
1.10.2 Carroll et al. (1984)	×		✓	
1.10.2 Caine et al. (1986)	×	✓		
1.10.2 Beatty et al. (1988)	×	✓		

Appropriateness: ~ reasonably appropriate with some reservations (see relevant section); × not appropriate

1.11 AIMS OF CURRENT RESEARCH

Previous research has demonstrated that deficits in recent verbal and visuo-spatial memory are a prominent cognitive characteristic of MS patients. However, the variety of memory assessments employed in these studies have been shown to possess various methodological flaws. In addition, due to the potential coexisting cognitive and/or physical disabilities of the patient group, many tasks are considered inappropriate for assessing memory function in MS. Therefore, the aim of this research is to develop a test of memory which will overcome the shortfalls of the conventional measures, providing an appropriate and comprehensive assessment tool to examine recent verbal and visuo-spatial memory in patients with MS. Specifically:

- The new test will minimise the effects of acquired language dysfunction, especially dysarthria, by utilising high frequency words and generous timing. As the items will be familiar, and there will be no time pressures, patients with poor articulation will be able to focus purely on the memory component of the task, without diverting processing resources to pronunciation. In addition, where possible, the opportunity to point or gesture, rather than speak, in order to indicate response choices, will facilitate responding.
- The task demands of the new test will not entail precise, co-ordinated hand movements. Thus patients with compromised manual dexterity will not be automatically handicapped.
- The visual disturbances experienced by some patients with MS will be accommodated by the use of large, distinct stimuli of low complexity, hence, good visual acuity, colour vision, etc. will not be necessary.

- The visual simplicity of the stimulus items will also attempt to accommodate patients with coincident cognitive difficulties, as fine perceptual discrimination will not be required.
- Attentional deficiencies will be addressed by presenting the stimuli visually, for an extended time, and asking the subject to make a decision regarding the stimuli. This will endeavour to ensure the items have been attended to, an essential staging post to memory.

The measures detailed above should overcome the specific difficulties of assessing memory function in patients with compromised sensori-motor skills, and/or coincident cognitive dysfunction. However, the technical shortcomings of many current neuropsychological tests must also be considered and if possible addressed.

- By increasing the number of items from one level to the next, the measure will span the target section of the ability spectrum, assessing memory capabilities from the moderately impaired to the bright intact. As there is already a comprehensive battery of memory tests for the severely memory impaired (The Camden Memory Tests, Warrington, 1996), and profound memory deficits are relatively uncommon in MS, the very bottom end of the ability spectrum will not be included in the target range of capabilities of the new measure. The Camden Memory Tests (Warrington, 1996) comprise five easy tasks for the older adult, which, due to the simplicity of the stimuli and task demands, are appropriate for the assessment of low level memory ability in the MS population.
- Equivalent tasks will be used in the verbal and visuo-spatial domains to assess recall, paired association, and recognition memory. The new test will therefore directly compare each of the three forms of memory for both verbal and visuo-spatial

modalities, attempting to minimise the format and content artefacts which arise when comparisons of various types of memory are made for an individual subject.

- Furthermore, the visuo-spatial stimuli will comprise items which are not easy to code verbally, providing a purer, more accurate assessment of visuo-spatial memory skills.

In order to assess the scientific properties and clinical appropriateness of the new test of memory, it will be administered to a sample of healthy controls, and a group of patients with MS.

- The standardisation sample will comprise a group of volunteers with no history of neurological or psychiatric disease, stratified for sex, age and IQ, and retired from or in full-time employment.
- The validation sample will constitute clinically definite MS patients with varying disease durations and levels of disability, who required ongoing attention from a consultant neurologist (i.e. MS patients attending hospital).

CHAPTER TWO: THE EXPERIMENTS

2.1 THE PILOT STUDIES

In order to assess whether various test stimuli and formats were fulfilling the aims outlined in Section 1.11, several, small pilot studies were conducted. A cycle of theoretical deliberation, test construction, administration to subjects, and discussion of results, was adopted for both the verbal and spatial sections of the new measure, such that some ideas of stimuli and format were eliminated, and others refined.

The pilot studies involved clinically definite MS patients with varying disease characteristics, who were recruited from the National Hospital for Neurology and Neurosurgery, and its Neuro-Rehabilitation Unit, and where appropriate, healthy controls who were friends of the author. All individuals were well informed of the purpose of the project, and of their role as pilot subjects. In most cases, subjects were recruited to participate in only one verbal and one spatial pilot study. If a subject was administered more than one version of the stimuli and/or tasks, the test sessions were separated by several days. Some of the MS patients recruited had undertaken a clinical cognitive assessment for the purposes of their hospitalisation, which included a number of conventional memory tasks. This information was available to the author. Thus, despite the limitations of these conventional measures with regard to physical disability and coincident cognitive defects, the degree of memory dysfunction in these cases could be roughly estimated, and used to calibrate performance on the pilot versions of the new memory test. As relatively detailed background data were available for the patient pilot

subjects, small numbers were recruited. The principal aim of these experiments was to provide data regarding the difficulty of the stimuli and tasks, and the small sample sizes involved permitted frequent alterations to both the stimulus items and test formats.

For the majority of pilot studies detailed in Sections 2.1.1 and 2.1.2, data from the recall memory, paired association, and recognition memory sections were examined simultaneously, even if the stimuli and the study and test phase formats for assessing a specific type of memory remained unaltered from a previous pilot study. This intentional, continuous appraisal of results from each memory domain afforded the opportunity to assess the relationship between the memory types within the verbal and spatial sections, and to evaluate the impact of changes to one section on the overall memory assessment, for the verbal or spatial modality. Throughout test development, consideration of the format for both the verbal and spatial sections was required, in an effort to devise matched assessments.

2.1.1 The Pilot Studies: Verbal Memory

Pilot Study V 1

i) Rationale: This study was designed to provide preliminary information of the task demands necessary to assess accurately three verbal memory domains, specifically: recall memory, paired association, and recognition memory.

iia) Materials And Methods: The subject was required to read aloud six pairs of semantically related words (e.g. bread - butter), which were individually presented to the subject. All items were AA (100 times or over per million) or A (50-99 times per million) frequency words (Thorndike & Lorge, 1944). The following assessment procedures were then adopted:

- recall memory: in the test phase, the subject was asked to repeat as many items as he or she could remember, in any order.
- paired association: in the test phase, the subject was given the first word of a target pair and asked to recall from memory, without prompts, the item with which it had been paired in the study period.
- recognition memory: in the test phase, the subject was shown a series of 12 individual words, and was required to respond "yes" to those previously seen, and "no" to previously unseen items. The distractors comprised words, which although presented separately, were intentionally, semantically related to each other (e.g. two distractors were "cow - milk").

iib) Subjects: Pilot Study V 1 involved 14 MS patients with a broad range of memory abilities on conventional tasks. The male:female ratio was 3:11, with a mean (SD) age of 42.8 (10.2) years.

iii) Results:

Table 2.1.1.1: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 1

	mean (SD)	range
RECALL (max. 12)	6.79 (2.01)	3-10
PAIRED ASSOCIATION (max. 6)	5.71 (0.83)	3-6
RECOGNITION (max. 12)	11.50 (1.02)	9-12

iv) Discussion: The test of recall memory demonstrated a good range of scores, and performance on this section correlated highly with scores on a conventional verbal recall task, which suggested that the new recall test was assessing the range of memory

abilities exhibited by the sample. That the recall section spanned a range of capabilities was expected, as, prior to the development of any verbal tasks, a review of both patient and control performance on published verbal, free recall memory tests provided a guide to the number of items necessary to discriminate ability. The paired association and recognition sections, however, demonstrated pronounced ceiling effects, and in the recognition test phase, this was emphasised by eight individuals who recorded no false positive or false negatives, that is, a perfect score. Using conventional verbal recognition memory tests, in which there were up to 50 items, the patient group demonstrated a range of abilities, therefore, despite the limitations of existing measures, it must be concluded that the verbal paired association and recognition memory tasks of Pilot Study V 1 comprised items that were not sufficiently difficult to discriminate acceptably across varying capabilities.

v) Action: As pairs of words with a deliberate semantic link are known to facilitate verbal paired association and recognition memory, future pilot studies utilised items without deliberate semantic associations. This decision was supported by considering the possible introduction of parallel forms of the new memory task; using word pairs intentionally associated by meaning, as in Pilot Study V 1, would require each version of the test to be standardised and validated separately, due to the difficulty of ensuring equality or uniformity of the semantic associations between items. Using words randomly selected from an item pool would allow the construction of parallel forms, without the specification of individual standardisation and validation of each version.

Pilot Study V 2

i) Rationale: This study was designed to provide further preliminary information of the task demands necessary to assess accurately three memory domains: recall memory,

paired association, and recognition memory, using stimuli with no intentional semantic associations.

iia) Materials And Methods: The stimuli comprised six pairs of words, each pair with no deliberate semantic link, selected from the AA (100 times or over per million) or A (50-99 times per million) frequency word lists of Thorndike and Lorge (1944). Recall memory, paired association, and recognition memory were assessed using the study and test phase formats detailed in Pilot Study V 1. The distractors used in the recognition test comprised a mixture of items that were deliberately, semantically related, and words with no obvious semantic link to the targets.

iib) Subjects: Pilot Study V 2 involved 11 MS patients with a broad range of memory abilities on conventional tasks. The male:female ratio was 3:8, and the mean (SD) age 42.5 (11.2) years.

iii) Results:

Table 2.1.1.2: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 2

	mean (SD)	range
RECALL (max. 12)	3.91 (1.81)	1-8
PAIRED ASSOCIATION (max. 6)	0.55 (0.82)	0-2
RECOGNITION (max. 12)	9.91 (2.02)	6-12

iv) Discussion: The assessment of recall memory again spanned a wide range of scores; however, performance on the paired association section appeared to demonstrate a floor effect. MS patients classed as intact on conventional verbal memory tasks were unable to score on this section, which suggested the task possessed poor discriminability. The

recognition memory section produced a better range of scores than Pilot Study V 1, although there was still a trend towards high scores, and hence a ceiling effect.

v) Action: The identification of the number of pairs of items necessary to grade a verbal paired association task at the lower end of the ability spectrum was required, in order to develop a sensitive assessment of this memory domain. In addition, redevelopment of the recognition memory task was undertaken to minimise the ceiling effect.

Pilot Study V 3

i) Rationale: This study was designed to examine the number of pairs of items required to grade a paired association task.

iia) Materials And Methods: The stimuli comprised pairs of words, each pair with no deliberately engineered semantic association, constructed as detailed in Pilot Study V 2. The subject was assessed using one, two, three, and four pairs of items; and recall memory, paired association, and recognition memory were examined using the test formats reported in Pilot Study V 1.

iib) Subject: Pilot Study V 3 involved one male MS patient, aged 39 years, with mild memory dysfunction on conventional tasks.

iii) Results:

Table 2.1.1.3: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 3

	1 pair of items	2 pairs of items	3 pairs of items	4 pairs of items
RECALL	2 (max. 2)	4 (max. 4)	4 (max. 6)	3 (max. 8)
PAIRED ASSOCIATION	1 (max. 1)	1 (max. 2)	0 (max. 3)	0 (max. 4)
RECOGNITION	2 (max. 2)	4 (max. 4)	5 (max. 6)	4 (max. 8)

iv) Discussion: On examination of the subject's performance on the pilot tasks, it can be seen that he scored well on all sections which involved one and two pairs of items; however, when three and four pairs of items were administered, his paired association score dropped to zero, a floor effect. Using three and four pairs of items, the recall and recognition sections appeared to give a good indication of the number of items required to discriminate ability at the lower end of the spectrum.

v) Action: The format of the paired association task required revision, to enable the graded assessment of ability across the target range. Consideration of the test procedure for the evaluation of recognition memory, and the demonstrated ease of the task, suggested that the "yes/no" format, that is, making judgements regarding whether items were familiar or previously unseen, would be more discerning if pairs of items, rather than individual words, were used. It was thought that this alteration would reduce the ceiling effect. In addition, consideration of the overall format of the verbal test sections suggested that using only one test of recall memory, paired association, and recognition memory, respectively, was insufficient to span the target range of abilities found in the MS population. Three Sets, comprising an increasing number of items were therefore introduced. It was thought that these Sets may provide sufficient discrimination of the variation in memory capabilities of MS patients, excluding only the most severely impaired (as detailed in Section 1.11). An advantage of using different difficulty levels, grading memory skills across the target ability spectrum, was that the more impaired patients would be prevented from struggling to complete tasks which would provide limited information of their capabilities.

Pilot Study V 4

i) Rationale: This study was designed to assess the test formats of the revised paired association and recognition sections. In addition, for the three memory domains, the sensitivity of three Sets, which comprised an increasing number of items, was also examined.

iia) Materials And Methods: Three, five, and seven pairs of words with no deliberate semantic association between pairs were constructed as detailed in Pilot Study V 2, and presented to the subject, each pair for three seconds. On presentation of the pairs, the subject was asked to decide whether the items were words they would use everyday. This ensured the subject had attended to the stimuli, an essential staging post to memory. On completion of the study period, the following assessments were conducted:

- recall memory: the test phase, as detailed in Pilot Study V 1.
- paired association: in the test phase, the subject was given the first word of a pair and asked to select from six choices, that with which it had been paired in the study phase. Different distractors were presented with each target second item of a pair. The distractors were taken from the same pool of stimuli detailed in Pilot Study V 2.
- recognition memory: in the test phase, the subject was shown a series of pairs of words, and was required to respond "yes" to those previously seen, and " no" to previously unseen pairs. The distractor pairs comprised one target word and one item which was intentionally, semantically related to the correct target. For example, if "air-baby" was the target pair, the relevant distractor pair would read "air-girl".

The recall, paired association and recognition sections involving the least number of items were referred to as Set A, Set B involved five pairs of items, and the sections using the most items were referred to as Set C.

iib) Subjects: Pilot Study V 4 involved two female MS patients, mean (SD) age 48.5 (13.4) years, with mild memory dysfunction on conventional tasks.

iii) Results:

Table 2.1.1.4: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 4

	mean (SD)	scores
Set A		
RECALL (max. 6)	5.00 (1.41)	4, 6
PAIRED ASSOCIATION (max. 3)	2.50 (0.71)	2, 3
RECOGNITION (max. 3)	3.00 (0.00)	3, 3
Set B		
RECALL (max. 10)	4.00 (1.41)	3, 5
PAIRED ASSOCIATION (max. 5)	4.50 (0.71)	4, 5
RECOGNITION (max. 5)	5.00 (0.00)	5, 5
Set C		
RECALL (max. 14)	6.00 (1.41)	5, 7
PAIRED ASSOCIATION (max. 7)	5.00 (0.71)	4, 6
RECOGNITION (max. 7)	5.50 (0.71)	5, 6

iv) Discussion: The recall sections of the three Sets, seemed appropriate for the two patients; Set A (comprising the least number of items), was comfortably within their capability, and as the number of pairs increased, the task appeared to become more

challenging. Scores on the paired association sections were high, but not at ceiling level, therefore it appeared that the revised test format was more appropriate, demonstrating no marked floor or ceiling effects. Both of the patients scored highly on all the recognition sections, which suggested that the task was still relatively easy and did not grade their ability accurately.

v) Action: The results of this pilot study suggested that the test formats of the recall, paired association, and recognition sections were appropriate for the patient group. However, as previously noted, the two patients were reported as exhibiting mild memory dysfunction on a conventional memory task, thus further data were required to evaluate accurately the sensitivity of the Sets, that is, to establish whether the increment in the number of items was of the appropriate magnitude. It was noted that in the recall sections subjects tended to spend relatively long periods of time attempting to retrieve both items of a pair, rather than simply as many words as they could remember. To prevent such stalling, individual words were used in the recall sections. The stimuli used in the test phase of the recognition sections comprised distractor pairs in which the incorrect item was intentionally, semantically related to the target word (e.g. target pair "air-baby"; distractor pair "air-girl"). As noted previously, the equality or uniformity of semantic associations cannot be precisely measured, and therefore, if parallel forms were to be introduced, separate standardisation and validation of each form would be necessary. All other sections were designed to avoid this requirement of potential parallel forms, and therefore the distractor pairs of the recognition sections were revised to comprise pairings without a deliberate semantic association to target items. In addition, it was noted that for each subject, the amount of time it took to administer the recall, paired association, and recognition sections, for each Set, was variable. This introduced an uncontrolled bias, and rendered comparison of scores across subjects of

limited value; it would be expected that the subject, who completed the recall and paired association sections more quickly, would attain higher scores on the recognition sections, than an individual taking a greater length of time on the initial tasks. To address this issue, novel items were used for each recall, paired association, and recognition section.

Pilot Study V 5

i) Rationale: This study was designed to evaluate a revised format for the verbal recall, paired association, and recognition sections, using novel stimuli for each section within each of the three Sets.

iia) Materials And Methods: All stimuli used in the recall, paired association, and recognition sections were randomly selected from a large pool of AA or A frequency words (Thorndike & Lorge, 1944). The pool was generated by applying a number of criteria which excluded: words of less than three or more than nine letters, numbers, proper nouns, pronouns, verbs, abbreviations, archaic items, and words with negative associations for chronically ill patients. In the study phase of each section, items were presented for three seconds, during which the subject was required to participate in the decision making process described in Pilot Study V 4. In the test phases, the order of item presentation was randomly determined. The following assessments were conducted:

- recall memory: the stimuli for the recall sections were six, 10, and 14 individual words, randomly selected from the large pool of items. Recall was assessed using the method described in Pilot Study V 1.
- paired association: presentation of three, five, and seven pairs of randomly selected words. Paired association memory was assessed using the method detailed in Pilot

Study V 4. The distractors were also randomly selected from the item pool, and the position of the target second word among the distractors was randomly assigned in each case.

- recognition memory: presentation of three, five, and seven pairs of randomly selected words. Recognition memory was assessed using the test phase format reported in Pilot Study V 4. The distractor pairs comprised one target item, not necessarily correctly positioned in the pair, and one randomly selected word. The choice of word to be paired with the distractor, and its position in the pairing were also randomly allocated.

Once a word had been removed from the pool, it was excluded for the rest of the selection process, for all sections. The order of item presentation in each test phase was randomly determined.

iib) Subjects: Pilot Study V 5 involved two MS patients with moderate memory deficits on conventional tasks. The male:female ratio was 1:1, and the mean (SD) age 31.0 (4.2) years. In addition, one healthy control was recruited (female, 48 years).

iii) Results:

Table 2.1.1.5: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 5

	mean (SD)	scores
Set A		
RECALL (max. 6)	3.00 (1.41)	2, 4
PAIRED ASSOCIATION (max. 3)	2.00 (1.41)	1, 3
RECOGNITION (max. 3)	2.00 (1.41)	1, 3

	mean (SD)	scores
Set B		
RECALL (max. 10)	4.00 (0.00)	4, 4
PAIRED ASSOCIATION (max. 5)	3.50 (2.12)	2, 5
RECOGNITION (max. 5)	4.50 (0.71)	4, 5
Set C		
RECALL (max. 14)	-	1
PAIRED ASSOCIATION (max. 7)	-	0
RECOGNITION (max.7)	-	3

Set C (seven pairs of items) was administered to one patient only

Table 2.1.1.6: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 5 For The Healthy Control

Set A	score	**Set B**	score	**Set C**	score
RECALL (max. 6)	6	RECALL (max. 10)	6	RECALL (max. 14)	8
PAIRED ASSOCIATION (max. 3)	3	PAIRED ASSOCIATION (max. 5)	4	PAIRED ASSOCIATION (max. 7)	7
RECOGNITION (max. 3)	3	RECOGNITION (max. 5)	3	RECOGNITION (max.7)	5

iv) Discussion: The revised format using different items for each recall, paired association, and recognition section within a Set was simple to administer, and did not appear to lead to an increase in reported interference effects. The three recall, paired

association, and recognition sections appeared to span the range of ability exhibited, becoming more challenging with the increment in the number of items.

As expected, the healthy control scored well on each section of the new test, for all three Sets. However, the fact that she did not attain a perfect score throughout, together with her subjective report of finding Set C (comprising the most items) relatively difficult, suggested that this final Set was reasonably challenging to an intelligent (NART-R IQ 125), intact individual. The scores of the patients and the healthy control, therefore, suggested that the recall, paired association, and recognition assessments were sensitive to a range of memory capabilities, from the moderately impaired to the bright normal.

v) Action: Further data was collected to evaluate the revised form of the recall, paired association, and recognition tasks. In addition, on reflection of the test format for the recognition memory sections, it was noted that the use of the "yes/no" format could potentially result in skewed data; a subject who answered either "yes" or "no" throughout would achieve a high score, coincident with a large number of false positives or negatives. To account for this, an "either/or" strategy, that is, the subject is required to select which of two pairs has been previously presented, was adopted for future pilot studies.

Pilot Study V 6

i) Rationale: This study was designed to assess the revised test format for the recognition sections, and collect further data on the whole verbal assessment, using the three Sets.

iia) Materials And Methods: For the recall and paired association sections, the stimuli and the format of the study and test phases were as detailed in Pilot Study V 5. For the

recognition sections, the target and distractor stimuli and the study period format were identical to those described in Pilot Study V 5. However, in the test phase, the subject was asked which pair of items he or she had seen previously (this contrasted with the previous "yes/no" response format of familiar and previously unseen items).

iib) Subjects: Pilot Study V 6 involved 13 MS patients with a broad range of memory abilities on conventional tasks. The male:female ratio was 6:7, and the mean (SD) age 42.4 (12.0) years. In addition, six healthy controls were recruited. The male:female ratio of the control group was 2:4, with a mean (SD) age of 49.7 (20.1) years.

iii) Results:

Table 2.1.1.7: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 6

	mean (SD)	range
Set A		
RECALL (max. 6)	4.46 (1.27)	2-6
PAIRED ASSOCIATION (max. 3)	1.73 (1.01)	0-3
RECOGNITION (max. 3)	2.55 (0.69)	1-3
Set B		
RECALL (max. 10)	2.50 (1.41)	0-5
PAIRED ASSOCIATION (max. 5)	3.13 (1.64)	0-5
RECOGNITION (max. 5)	4.13 (1.13)	2-5

	mean (SD)	range
Set C		
RECALL (max. 14)	3.00 (1.41)	2, 4
PAIRED ASSOCIATION (max. 7)	6.50 (0.71)	6, 7
RECOGNITION (max.7)	7.00 (0.00)	7, 7

Set B (five pairs of items) was administered to eight patients only
Set C (seven pairs of items) was administered to two patients only

Table 2.1.1.8: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 6 For The Control Subjects

Set A	mean (SD)	range	**Set B**	score
RECALL (max. 6)	5.33 (1.21)	3-6	RECALL (max. 10)	2
PAIRED ASSOCIATION (max. 3)	1.60 (1.34)	0-3	PAIRED ASSOCIATION (max. 5)	0
RECOGNITION (max. 3)	2.80 (0.45)	2-3	RECOGNITION (max. 5)	3

Set B (five pairs of items) was administered to one individual (male, 66 years)

iv) Discussion: As suggested by the results of Pilot Study V 5, the new recall and paired association tasks appeared to span the range of ability estimated from conventional memory tests. The revised format of the recognition sections was simple to administer and produced a range of scores, which suggested discriminability. The scores of the two patients who completed Set C (comprising the most items), appeared to suggest a ceiling effect on the paired association and recognition sections. (It was noted, however, that the subjects both possessed above average intelligence, mean NART-R IQ 112, and intact, probably above average memory skills.)

As expected, the performance of the healthy controls on the recall, paired association, and recognition sections of Set A (comprising the least number of items), suggested that the task demands were comfortably within their capabilities. The ages of the subjects were diverse (26-79 years), thus Set A appeared applicable across the adult age range. The scores of the individual who completed Set B seemed to suggest that the number of items was also appropriate for assessing memory in older subjects, where memory skills are prone to deteriorate.

v) Action: On consideration of the pilot results of the three paired association and recognition sections, and the fact that some healthy controls can comfortably score 50/50 on the Recognition Memory Test For Words (Warrington, 1984), the number of items in the final paired association and recognition sections was increased.

Pilot Study V 7

i) Rationale: This study was designed to evaluate the addition of a further two pairs of items to the final verbal paired association and recognition sections.

iia) Materials And Methods: The stimuli, study and test phase formats detailed in Pilot Study V 6 were employed throughout, with the addition of a further two items to the final paired association and recognition sections. Thus there were nine pairs of items in these two sections, whereas Pilot Study V 6 utilised seven pairs.

iib) Subject: Pilot Study V 7 involved one female MS patient, aged 31 years, with intact memory skills on conventional tasks.

iii) Results:

Table 2.1.1.9: Results On The Verbal Recall, Paired Association, And Recognition Tasks Of Pilot Study V 7

Set A	score	**Set B**	score	**Set C**	score
RECALL (max. 6)	6	RECALL (max. 10)	3	RECALL (max. 14)	10
PAIRED ASSOCIATION (max. 3)	3	PAIRED ASSOCIATION (max. 5)	4	PAIRED ASSOCIATION (max. 9)	8
RECOGNITION (max. 3)	3	RECOGNITION (max. 5)	5	RECOGNITION (max. 9)	9

iv) Discussion: As expected, this patient scored well on all sections of the new test, which suggested that the tasks were perhaps not quite sensitive enough at the top end of the ability spectrum. However, as she was of above average intelligence, and considering the results from Pilot Studies V 6 and V 5, the verbal sections of the test were considered adequately prepared for formal assessment of the target population.

Conclusions

The pilot studies of verbal memory detailed in Section 2.1.1 illustrated some of the difficulties inherent in neuropsychological test development: the tasks must grade ability across a wide spectrum of memory skills, without demonstrating pronounced floor or ceiling effects for the target population. Moreover, throughout testing the sensori-motor deficits of the patient group must be considered. The structure of the verbal sections detailed in Pilot Study V 7 appeared to accommodate these theoretical and practical criteria: patients with language difficulties were able to indicate their responses on the paired association and recognition tasks, if a spoken response was effortful. In addition, for all the study and test sections, items were presented visually, in

a large, bold, well spaced format, which attempted to accommodate patients with attentional difficulties, without penalising patients who may have had poor visual acuity. The three Sets of the new assessments, comprising an increasing number of items, for the assessment of recall memory, paired association, and recognition memory also seemed to span the target ability spectrum.

2.1.2 The Pilot Studies: Spatial Memory

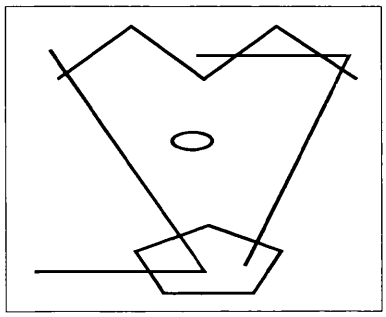
Pilot Study S 1

i) Rationale: This study was designed to provide preliminary information of the type of stimuli which would fulfil the criteria outlined in Section 1.11, that is, visually simple items which could not be coded verbally.

iia) Materials And Methods: The subject was required to study six pairs of spatial stimuli, each pair presented for three seconds. An example of the stimuli used is shown in Figure 2.1.2.1. In the test phase, the subject was asked to point to the items previously presented, from 24 choices. There were three sets of six pairs.

iib) Subjects: Pilot Study S 1 involved two MS patients with mild memory dysfunction on conventional tasks. The male:female ratio was 1:1, and the mean (SD) age 44.5 (5.0) years.

Figure 2.1.2.1: An Example Of The Stimuli Used In Pilot Study S 1



iii) Results:

Table 2.1.2.1: Results Of Pilot Study S 1

	mean (SD)	scores
set 1 (max. 12)	5.50 (2.12)	4, 7
set 2 (max. 12)	4.00 (1.41)	3, 5
set 3 (max. 12)	5.00 (2.83)	3, 7

iv) Discussion: The number of items seemed appropriate for the two patients, who, as noted previously, exhibited mild memory dysfunction on a conventional assessment. However, consideration of the actual form of the stimuli, and subjective reports from the subjects regarding how they had performed the task, suggested that the items could be coded verbally (using names, e.g. "face" or "spaceship"; or using names of objects as a form of coding, e.g. "hexagon and triangle with a circle in the middle"), and did not fulfil the specified criteria of applicability to patients with poor visual acuity. In addition, despite careful deliberation, devising suitable tasks of recall, paired association, and recognition memory using these items remained problematic.

v) Action: Spatial stimuli without the above disadvantages were developed, which were appropriate to assess recall memory, paired association, and recognition memory in patients with compromised sensori-motor skills, and span the target range of ability detailed in Sections 1.11.

Pilot Study S 2

i) Rationale: This study was designed to evaluate the structure of the revised spatial stimuli and assess the format, using three Sets (comprising an increasing number of items), of spatial recall memory, paired association, and recognition memory tasks.

iia) Materials And Methods: The stimuli comprised three, five, and seven pairs of irregular shapes, generated on a computer using the graphics package Corel Draw 6.0 (Corel Corporation, 1988-1995), which runs through Windows '95. An example of the shapes is given in Figure 2.1.2.2. Each pair of items was presented for four seconds, during which the subject was asked to respond "yes" or "no" to the question "is this a good design for wallpaper?". Answering this question ensured that the subject had attended to the items, an essential staging post to memory. On completion of the study period the following assessments were conducted:

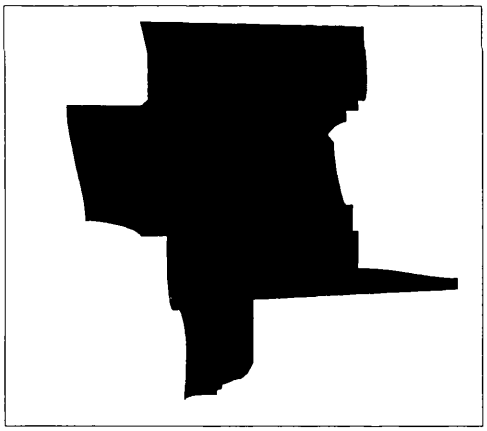
- recall memory: in the test phase, each shape had been vertically bisected, and the subject was given either the right hand or left hand segment. He or she was then required to choose, from six alternatives, the correct target half, to complete the item. Recall memory for each individual shape was assessed using six novel choices on each trial. Which half of the target item the subject was given, and the position of the complementary target piece among the five distractors were randomly assigned.
- paired association: in the test phase, the subject was given the first shape of a pair, that is, the one on the left as the subject observed them, and asked to select from six choices, that with which it had been paired in the study period. The position of the second target among the five distractors was decided using randomisation.
- recognition memory: in the test phase, the subject was shown a series of pairs of shapes, and required to respond "yes" to those previously seen, and " no" to previously unseen items. The distractor pairs comprised one target item, not

necessarily correctly positioned in the pair, and one previously unseen item. The target shape paired with the distractor, and its position in the pairing were randomly allocated.

All distractors were developed using the same method detailed for the target stimuli. Randomisation was employed to determine the order of item presentation in each test phase. The recall, paired association, and recognition sections involving the least number of items were referred to as Set A, Set B comprised five pairs of items, and the sections using the most items was referred to as Set C.

iib) Subjects: Pilot Study S 2 involved two, female MS patients, mean (SD) age 48.5 (13.4) years, with mild memory dysfunction on conventional tasks.

Figure 2.1.2.2: An Example Of The Stimuli Used In Pilot Study S 2



iii) Results:

Table 2.1.2.2: Results On The Spatial Recall, Paired Association, And Recognition Tasks Of Pilot Study S 2

	mean (SD)	scores
Set A		
RECALL (max. 6)	4.50 (0.71)	4, 5
PAIRED ASSOCIATION (max. 3)	1.00 (0.00)	1, 1
RECOGNITION (max. 3)	2.00 (0.00)	2, 2
Set B		
RECALL (max. 10)	6.00 (1.41)	5, 7
PAIRED ASSOCIATION (max. 5)	2.00 (0.00)	2, 2
RECOGNITION (max. 5)	3.50 (0.71)	3, 4
Set C		
RECALL (max. 14)	7.00 (1.41)	6, 8
PAIRED ASSOCIATION (max. 7)	3.50 (0.71)	3, 4
RECOGNITION (max. 7)	4.00 (0.00)	4, 4

iv) Discussion: The increment in the number of items with each Set seemed appropriate for the two patients: Set A was comfortably within the capability of the two subjects, and as the number of pairs increased, the task appeared to become more challenging. Scores on the paired association and recognition sections seemed to demonstrate the

same pattern, which suggested the grading of ability, and an absence of ceiling effects. However, a number of fundamental flaws were identified, as detailed in the actions.

v) Action: The results of this pilot study suggested that the structure of the recall, paired association, and recognition tasks were appropriate for the patient group. However, the use of irregular items, drawn using the mouse, created a number of very detailed, precise characteristics which could only be viewed by subjects with good vision. As applicability to patients with limited visual acuity was a prerequisite of the new measure, the stimuli were revised. In addition, the use of stimuli created free hand did not control for uniformity in salience or visual complexity, hence each version of such a task would need to be individually standardised and validated if parallel forms were to be devised. Regulation of stimuli was introduced to avoid separate standardisation and validation of potential parallel versions. As detailed in Pilot Study V 4 a notable difference in the amount of time it took to administer the recall, paired association, and recognition sections for each Set was recorded. To overcome this problem, novel items were used for each recall, paired association, and recognition section. Specific to the recall test sections; the use of a vertical bisection through the targets and the distractors, may have allowed the subject to perform well on the tasks simply by identifying, from the six choices, the item which provided a perfect join between the left hand and right hand pieces. This weakness was overcome in a revised recall section. Finally, the two patients were reported as exhibiting mild memory dysfunction on a conventional memory task, further data were therefore required to evaluate the sensitivity of the increment in the number of items.

Pilot Study S 3

i) Rationale: This study was designed to evaluate the revised spatial stimuli, and assess the strategy of using different pairs of items for each recall, paired association, and recognition section, within each of the three Sets.

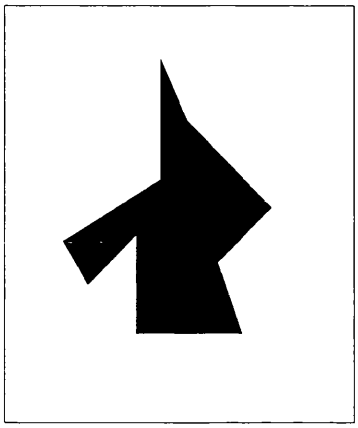
iia) Materials And Methods: The stimuli comprised three, five, and seven pairs of irregular shapes, generated on a computer using the graphics package Corel Draw 6.0 (Corel Corporation, 1988-1995), which runs through Windows '95. These items were created by plotting random co-ordinates (horizontal reference/vertical reference) on a sheet of 50 squares x 50 squares computerised graph paper. 10 co-ordinates were generated for each shape, and these were joined using the Bezier mode (straight lines) and a rule of minimal perimeter, to make irregular spatial stimuli. An example of the shapes is given in Figure 2.1.2.3. The study phase presentation and decision procedure were the same as those detailed in Pilot Study S 2. The following assessments were then carried out:

- recall memory: in the test phase, each shape had been bisected down one of four planes: vertical (|), horizontal (-) or one of the two diagonals (/ or \ ). The orientation of the bisection was randomly selected. The two co-ordinates at either end of the bisecting line were identified and used as markers for the distractors. In addition, the number of points in the target half of the shape, to be identified, were counted and the distractors comprised the same number of points. The format of the test phase was the same as that detailed in Pilot Study S 2.
- paired association and recognition memory: the test phase formats were the same as those recorded in Pilot Study S 2.

A different set of pairs was used for each recall, paired association, and recognition section.

iib) Subjects: Pilot Study S 3 involved two MS patients with mild memory dysfunction on conventional tasks. The male:female ratio was 1:1, and the mean (SD) age 31.0 (4.2) years. In addition, two, female, healthy controls were recruited. Their mean (SD) age was 40.5 (10.6) years.

Figure 2.1.2.3: An Example Of The Stimuli Used In Pilot Study S 3



iii) Results:

Table 2.1.2.3: Results On The Spatial Recall, Paired Association, And Recognition Tasks Of Pilot Study S 3

	mean (SD)	scores
Set A		
RECALL (max. 6)	1.00 (0.00)	1, 1
PAIRED ASSOCIATION (max. 3)	2.00 (1.41)	1, 3
RECOGNITION (max. 3)	2.00 (0.00)	2, 2
Set B		
RECALL (max. 10)	1.00 (1.41)	0, 2
PAIRED ASSOCIATION (max. 5)	2.50 (0.71)	2, 3
RECOGNITION (max. 5)	2.00 (1.41)	1, 3

	mean (SD)	scores
Set C		
RECALL (max. 14)	-	3
PAIRED ASSOCIATION (max. 7)	-	1
RECOGNITION (max. 7)	-	0

Set C (seven pairs of items) was administered to only one patient

Table 2.1.2.4: Results On The Spatial Recall, Paired Association, And Recognition Tasks Of Pilot Study S 3, For The Two Control Subjects

	mean (SD)	scores
Set A		
RECALL (max. 6)	1.00 (0.00)	1, 1
PAIRED ASSOCIATION (max. 3)	1.50 (0.71)	1, 2
RECOGNITION (max. 3)	2.50 (0.71)	2, 3

	mean (SD)	scores
Set B		
RECALL (max. 10)	-	1
PAIRED ASSOCIATION (max. 5)	-	1
RECOGNITION (max. 5)	-	1
Set C		
RECALL (max. 14)	-	2
PAIRED ASSOCIATION (max. 7)	-	3
RECOGNITION (max. 7)	-	4

Sets B and C were completed by only one individual (48 years)

iv) Discussion: Both the patient and control pilot subjects performed poorly on Sets B and C for recall, paired association, and recognition memory. The patients who exhibited mild memory deficits on a conventional task, did not appear to score at a level notably different to the controls, which suggested that the tasks possessed poor discriminability. Consideration of the stimuli and subjective reports from the participants suggested that the items were too visually complicated to allow encoding within the exposure period.

v) Action: The results of this pilot study suggested that the stimuli were too complex to assess accurately spatial recall, paired association, and recognition memory. Further revisions were made. The structure of the test phase formats of the paired association and recognition sections appeared suitable for the patient group, and complemented the verbal sections. However, the recall task was considered inappropriate for patients with

poor manual dexterity. In addition, it was noted that although the co-ordinates at the bisection points were identical for the target and distractors, if the correct half was selected from the six choices, placing the two pieces together created a continuous line. However, choosing any of the five distractors, and placing the two pieces together formed an additional corner. Further revisions were conducted to create an appropriate spatial recall memory task. The recognition sections used the "yes/no" format, which as detailed in Pilot Study V 5 could potentially result in skewed data. Equivalent action to that noted in V 5 was taken, that is, the use of an "either/or" strategy in the assessment of recognition memory.

Pilot Study S 4

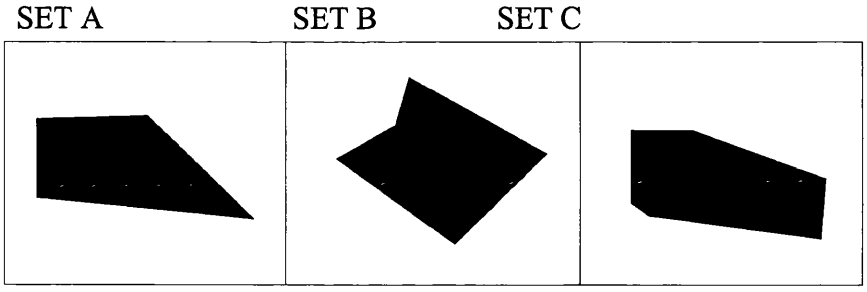
i) Rationale: This study was designed to assess the revised stimuli and format for the paired association and recognition sections using the three Sets.

iia) Materials And Methods: The stimuli consisted of irregular shapes, constructed by generating a series of random co-ordinates and plotting them as detailed in Pilot Study S 3. However, for the pairs of items used in the paired association and recognition tasks of Set A, four co-ordinates were generated for each shape, with the additional rule that these should be located within different quadrants of the graph paper. For Set B, each item comprised five co-ordinates, and for Set C, six co-ordinates per shape were generated. Figure 2.1.2.4 provides an example of the items for each Set. The question used in the decision making process detailed in Pilot Study S 2 was altered to read "would you be able to draw these items, if required?", which was considered more suitable than that used previously (it must be noted that there was never any intention of the subject actually drawing the items). The response and the purpose of the procedure remained the same. The paired association test phase format was the same as that

detailed in Pilot Study S 2. For the recognition sections, the distractor pairs were constructed using the same randomisation process described in Pilot Study S 2, however, in the test phase, the subject was asked which pair of items, he or she had seen previously (this contrasted with the previous "yes/no" response format of familiar and unseen items).

iib) Subjects: Pilot Study S 4 involved 11 MS patients with a broad range of memory abilities on conventional tasks. The male:female ratio was 5:6, with a mean (SD) age of 40.9 (12.6) years. In addition, six healthy controls were recruited. The male:female ratio of the control group was 2:4, and the mean (SD) age 49.7 (20.1) years.

Figure 2.1.2.4: An Example Of The Stimuli Used In Pilot Study S 4



iii) Results:

Table 2.1.2.5: Results On The Spatial Paired Association, And Recognition Tasks Of Pilot Study S 4

	mean (SD)	range
Set A		
PAIRED ASSOCIATION (max. 3)	1.80 (0.79)	1-3
RECOGNITION (max. 3)	2.18 (0.60)	1-3
Set B		
PAIRED ASSOCIATION (max. 5)	1.43 (0.53)	1-2
RECOGNITION (max. 5)	3.00 (1.07)	2-5
Set C		
PAIRED ASSOCIATION (max. 7)	3.50 (0.71)	3-4
RECOGNITION (max. 7)	5.50 (0.71)	5-6

Set B (five pairs of items) was administered to seven patients only
Set C (seven pairs of items) was administered to two patients only

Table 2.1.2.6: Results On The Spatial Paired Association, And Recognition Tasks Of Pilot Study S 4 For The Control Subjects

Set A	mean (SD)	range
PAIRED ASSOCIATION (max. 3)	1.40 (1.34)	0-3
RECOGNITION (max. 3)	2.00 (0.55)	2-3

Set B (five pairs of items) and Set C (seven pairs of items) were not administered to the healthy control subjects

iv) Discussion: The scores of the patients and the controls appeared to suggest that the spatial paired association and recognition sections spanned the range of memory abilities estimated using conventional tasks, without demonstrating floor or ceiling effects. As expected the performance of the healthy controls on Set A suggested that the task was within their capabilities, and was sensitive to memory capabilities across the age range.

v) Action: On consideration of the pilot results above, and the verbal paired association and recognition memory scores detailed in V 6, to enable the verbal and spatial tasks to match throughout, the number of items in the final paired association and recognition sections was increased to nine.

Pilot Study S 5

i) Rationale: This study was designed to evaluate the addition of a further two pairs of items to the final spatial paired association and recognition sections.

iia) Materials And Methods: The stimuli, study and test phase formats detailed in Pilot Study S 4 were employed throughout, with the addition of a further two items to the final paired association and recognition sections. Thus there were nine pairs of items, whereas Pilot Study S 4 involved seven pairs.

iib) Subjects: Pilot Study S 5 involved one, female MS patient, aged 31 years, with intact memory ability on conventional tasks.

iii) Results:

Table 2.1.2.7: Results On The Spatial Paired Association, And Recognition Tasks Of Pilot Study S 5

Set A	score	**Set B**	score	**Set C**	score
PAIRED ASSOCIATION (max. 3)	1	PAIRED ASSOCIATION (max. 5)	3	PAIRED ASSOCIATION (max. 9)	3
RECOGNITION (max. 3)	3	RECOGNITION (max. 5)	2	RECOGNITION (max. 9)	4

iv) Discussion: The patient scored reasonably well on the paired association and recognition tasks for the three Sets, but did not reach ceiling level, which suggested that the new spatial paired association and recognition sections were sensitive at the top end of the ability spectrum. Together with the results of Pilot Study S 4, the spatial paired association and recognition memory tasks of the new assessment were considered sufficiently prepared for formal assessment of the target population.

Pilot Study S 6

i) Rationale: This study was designed to evaluate the revised spatial stimuli of the recall section.

iia) Materials And Methods: The six items each comprised three bars, created by plotting three sets of two random co-ordinates (horizontal reference/vertical reference) on the computerised graph paper detailed in Pilot Study S 2. The subject was required to study each item for four seconds. In the test phase, two of the bars were provided, for each item, and the subject was asked to place a replica bar, in the position of the third, for a given target.

For each item, the position of the bar was scored from zero to five: a score of five was awarded if the whole of the bar was located within a zone 1cm around the exact position; a score of four was given if the bar was within a zone 2cm around the correct position; and so on up to a maximum zone of 5cm around the exact position, for which the patients was awarded one point (Figure 2.1.2.6 provides an example of the zones). The number of points allocated for a given item was dependant on the part of the bar in the furthest zone (e.g. if the majority of the bar fell in the zone 3cm from the target position, with one end in the zone 4cm away, 2 points were awarded, not 3). If any part of the bar fell outside the zones, a score of zero was allocated. On examination of the data, scores of three, four, or five were taken to indicate the correct position of the bar, when points were summated to give a total out of six. This criterion was chosen because, it was noted that if a subject did place the bar correctly, in the majority of cases the positioning was within 3cm of the exact location.

iib) Subjects: Pilot Study S 6 involved one, male MS patient, aged 48 years, with mild memory dysfunction on conventional tasks. In addition, six healthy controls were also recruited. The male: female ratio of the control group was 2:4, and the mean (SD) age 46.4 (20.6) years.

Figure 2.1.2.5: An Example Of The Stimuli Used In Pilot Study S 6

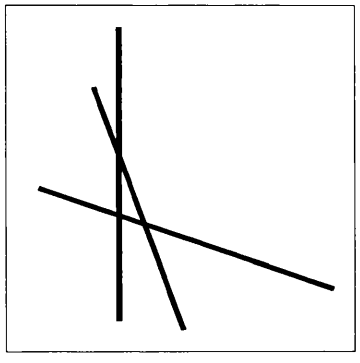
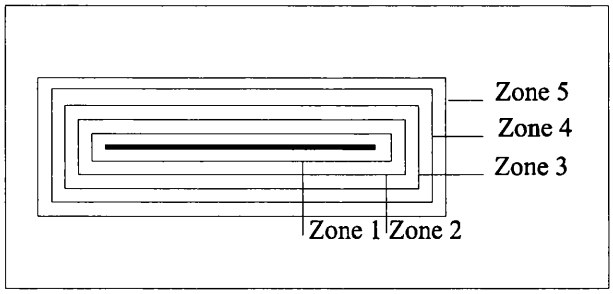


Figure 2.1.2.6: An Example Of The Zones Used In The Scoring System Of Pilot Study S 6



iii) Results:

The patient scored 0

Table 2.1.2.8: Results On The Spatial Recall Task Of Pilot Study S 6 For The Control Subjects

	mean (SD)	range
RECALL (max. 6)	0.60 (0.89)	0-2

iv) Discussion: The performance of both the patient and the controls suggested that the task was too difficult, as a pronounced floor effect was demonstrated.

v) Action: The structure of the stimuli, that is, placing a bar to create a given target was considered appropriate as a test of spatial recall memory and was further developed.

Pilot Study S 7

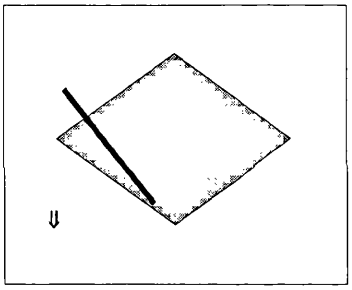
i) Rationale: This study was designed to evaluate modifications to the spatial recall stimuli and the test procedure.

iia) Materials And Methods: The stimuli were developed using the graphics package Corel Draw 6.0 (Corel Corporation, 1988-1995). They comprised six, regular background shapes, on each of which was superimposed a randomly positioned bar (an

example is shown in Figure 2.1.2.7). The length of the bar was maintained throughout the six recall trials, and the position determined by random co-ordinates, in each case. Three test conditions were administered to the subject. In each case the study period lasted four seconds, recall was then assessed following presentation of the complete series (condition 1), immediately after the presentation of each item (condition 2), and again on completion of this second condition (condition 3). The scoring system employed was the same as that reported in Pilot Study S 6.

iib) Subjects: Pilot Study S 7 involved one, male MS patient, aged 36 years, with mild memory deficits on conventional tasks.

Figure 2.1.2.7: An Example Of The Stimuli Used In Pilot Study S 7



iii) Results:

Table 2.1.2.9: Results On The Spatial Recall Task Of Pilot Study S 7

	score
Condition 1 (max. 6)	1
Condition 2 (max. 6)	6
Condition 3 (max. 6)	3

iv) Discussion: The patient scored poorly on condition 1, and, as expected, attained the maximum score on condition 2. Condition 3 appeared to produce an appropriate score for the task.

v) Action: The stimuli were considered appropriate, although slight alterations to the task were made.

Pilot Study S 8

i) Rationale: This study was designed to assess the revised format of the recall test phase, using two Sets, with an increment in the number of items.

iia) Materials And Methods: The construction of the stimuli was the same as that detailed in Pilot Study S 7. In the study phase, the subject was required to copy the position of the bar, having been provided with the background shape and a replica bar. In the test phase, the subject was asked to reposition the bar on a given shape, from memory. Set A involved six, individually presented stimuli and Set B comprised 10 items. Recall was assessed following the copying of all items in a Set. The scoring criteria detailed in Pilot Study S 6 was adopted, hence Set A was out of 6, and the maximum score on Set B was 10.

iib) Subjects: Pilot Study S 8 involved five MS patients with a range of memory capabilities on conventional tasks. The male:female ratio was 2:3, and the mean age (SD) 44.8 (7.9) years. In addition, two control subjects were recruited. The male:female ratio of these was 1:1, and the mean (SD) age 49.0 (24.0) years.

iii) Results:

Table 2.1.2.10: Results On The Spatial Recall Task Of Pilot Study S 8

	mean (SD)	range
Set A RECALL (max. 6)	2.40 (1.52)	0-4
Set B RECALL (max. 10)	1.00 (1.41)	0-2

Table 2.1.2.11: Results On The Spatial Recall Task Of Pilot Study S 8 For The Control Subjects

	scores
Set A RECALL (max. 6)	0, 3

Set B (10 items) was not administered to the healthy control subjects

iv) Discussion: The results of the patients and controls appeared to suggest that the task was still very difficult, and suggested that severely impaired patients may be unable to score, that is, they may demonstrate a floor effect.

v) Action: On consideration of the above results a further modification to the recall test format was made.

Pilot Study S 9

i) Rationale: This study was designed to evaluate a modified format for the test phase of the spatial recall section, using three Sets, which comprised an increasing number of items.

iia) Materials And Methods: The stimuli and the copying procedure were the same as those detailed in Pilot Study S 8, however, the subject was only required to copy three or four items, and then recall was assessed. On Set A, recall was tested after three target items had been presented. For Set B, as there were 10 stimuli, the shapes were copied and assessed as a set of three, four, and then three again. Set C entailed the copying and recall assessment being conducted with a set of three, two sets of four, and then three again. The order in which the items were examined in the test phase was randomly allocated. The scoring method detailed in Pilot Study S 6 was employed.

iib) Subjects: Pilot Study S 9 involved six MS patients with intact memory abilities/mild deficits on conventional tasks. The male:female ratio was 2:4, and the mean (SD) age 29.7 (10.5) years.

iii) Results:

Table 2.1.2.12: Results On The Spatial Recall Task Of Pilot Study S 9

	mean (SD)	range
Set A RECALL (max. 6)	4.17 (1.17)	3-6
Set B RECALL (max. 10)	4.00 (1.55)	3-7
Set C RECALL (max. 14)	10.33 (1.15)	9-11

Set C was completed by 3 patients only

iv) Discussion: The revised format for assessing spatial recall memory appeared to be sensitive across the range of abilities exhibited. The performance of the subjects on Set C may have been rather higher than predicted from the Sets A and B results, however,

as previously noted, the individuals who completed this section were of above average intelligence and exhibited no memory deficits. It may be that the more challenging task tends to elicit a more competent performance. Consideration of these results suggested that the recall section was sufficiently prepared for formal assessment of the target population.

Conclusions

The pilot studies of spatial memory detailed in Section 2.1.2 demonstrated the problems of developing a new measure, required to assess a range of memory domains, span the target ability spectrum, and accommodate the limited sensori-motor skills of the patient group. The structure of the spatial sections of the new assessment appeared to take into account all these theoretical and practical considerations: there were minimal manual dexterity requirements in the recall sections, and the paired association and recognition sections placed no demands on upper limb function. For the study and test phases of all sections, the items comprised large, visually simple, well spaced stimuli, which attempted to minimise the necessity for attention to be maintained, without penalising patients who may have poor visual acuity. The assessments of recall memory, paired association, and recognition memory over three Sets, with an increment in the number of items, also appeared to span the target ability spectrum. The structure of the spatial sections complemented that of the verbal elements, and, when examined holistically the test appeared to provide a comprehensive measure of both verbal and spatial recall memory, paired association, and recognition memory.

2.2 NEW TEST OF MEMORY: CONSTRUCTION

2.2.1 Task Familiarisation:

Task Familiarisation is the initial training phase which precedes the testing of a particular cognitive skill. Plohmann et al. (1998) demonstrated that initial training on specific attentional tasks greatly improved performance, and provided the opportunity to minimise the practice effects associated with learning the actual tasks, prior to the measurement of attentional capabilities. The effect of task familiarisation on test performance has also been shown in memory assessments, where scores on parallel forms of the Selective Reminding Test (Bushke & Fuld, 1974) only improved between the first and second trials (one week apart), but not on subsequent weekly testing (Hannay & Levin, 1985). This again demonstrates the importance of learning the procedural aspects of the actual task initially, in order to allow accurate assessment of a specific cognitive ability. It also suggests that just one trial is sufficient to acquire familiarity of the memory task demands. Clinically, the impact of task familiarisation on test performance has been acknowledged, and an initial task training phase is employed in the Advanced Progressive Matrices (Raven, 1962; Raven et al., 1983), and is used by Langdon and Warrington (1995) in the Verbal And Spatial Reasoning Test (VESPAR).

Since the verbal and spatial sections of the New Test Of Memory comprised a variety of procedures, and the spatial stimuli were abstract and unusual shapes, an initial task familiarisation phase was considered beneficial. Task familiarisation provides the opportunity for subjects to develop strategies, to aid retrieval of the stimuli, and for variance due to task practice effects to be accommodated, prior to the actual memory assessment. The use of a task familiarisation phase was not piloted in Section 2.1 because of the relatively small numbers of subjects involved in these preliminary

studies, and the emphasis placed on identifying appropriate stimuli and test formats which minimised the coincident physical and cognitive deficits characteristic of the target patient group, as discussed in Section 1.4. Subjects were deliberately not informed that the initial verbal and spatial sections were for the purposes of task familiarisation, to ensure that they exerted maximum effort, and hence learnt the tasks to their optimum ability. Feedback on memory performance was not provided, as it was considered of little value to inform the subject of their preliminary scores. However, if the task was performed incorrectly, the Task Familiarisation stage provided the opportunity for further rehearsal of the procedures. Since test conditions were identical in the initial training phase to those throughout the test sets, and procedural memory or the ability to learn the actual task does impact on overall memory ability, the scores on the Task Familiarisation stage were included in the composite totals.

2.2.2 Domains And Levels Of Difficulty:

The New Test Of Memory comprises matched verbal and spatial sections, with an initial Task Familiarisation stage followed by two levels of difficulty. The Task Familiarisation and the two difficulty levels each have three sections. The format of the test is summarised in Figure 2.2.1. Specifically, the three stages are referred to as

- Task Familiarisation, involving a small number of items
- Set 1, involving an intermediate number of items
- Set 2, involving the greatest number of items

The Task Familiarisation and both difficulty levels each comprise three sections which address

- recall memory (RCLL)

- paired association (PA)
- recognition memory (RECOG)

The verbal and spatial recall sections of the Task Familiarisation stage utilise six individual items, while the Task Familiarisation paired association and recognition subtests involve three pairs of stimuli. Set 1 recall contains 10 stimulus items, with the paired association and recognition sections using five pairs of items. There are 14 individual items for the Set 2 recall sections and nine pairs of stimuli involved in the Set 2 paired association and recognition subtests.

Figure 2.2.1: The Format Of The New Test Of Memory

	VERBAL SECTIONS	VERBAL SET TOTALS	SPATIAL SECTIONS	SPATIAL SET TOTALS
TF	RCLL (6 items) PA (3 pairs) RECOG (3 pairs)	12	RCLL (6 items) PA (3 pairs) RECOG (3 pairs)	12
SET 1 (easier level)	RCLL (10 items) PA (5 pairs) RECOG (5 pairs)	20	RCLL (10 items) PA (5 pairs) RECOG (5 pairs)	20
SET 2 (harder level)	RCLL (14 items) PA (9 pairs) RECOG (9 pairs)	32	RCLL (14 items) PA (9 pairs) RECOG (9 pairs)	32
DOMAIN TOTALS:	VERBAL RCLL: 30 PA: 17 RECOG: 17	COMPOSITE VERBAL TOTAL: 64	SPATIAL RCLL: 30 PA: 17 RECOG: 17	COMPOSITE SPATIAL TOTAL: 64 **OVERALL TOTAL: 128**

TF = Task Familiarisation; RCLL = recall memory; PA = paired association; RECOG = recognition memory

2.2.3 Verbal Sections:

The verbal stimuli for all sections of the New Test Of Memory were randomly selected from a pool of 1413 AA (100 times or over per million) or A (50-99 times per million) frequency words (Thorndike & Lorge, 1944). The exclusion criteria were as follows:

- words comprising less than three or more than nine letters
- items which spell numbers, for example, "two"
- words which are proper nouns, such as, names of people or places
- words which are pronouns, for example, "he" or "she"
- items which are verbs, for example, "sews"
- items which are abbreviation, for example, "hadn't" or "you're"
- words considered by the author to be archaic, for example, "thou"
- words considered by the author to evoke particularly negative associations for chronically ill patients, for example, "pain" or "death"

Words were only removed from the item pool if they exclusively fulfilled any of the above criteria without possessing another property not listed above, for example, "china" should be eliminated from the item pool because it is a proper noun, however it is also a regular noun and therefore avoids exclusion. Likewise, words with dual syntax, that is, those that are both nouns and verbs, for example, "walk" were not removed, neither were prepositions, for example, "although" or "between".

Once a word had been randomly selected from the pool, it remained excluded until item selection for the Task Familiarisation stage and both Sets had been completed. Therefore, a word had the potential to appear only once throughout the whole task. This avoided the possibility of the same word appearing as either a target or

distractor, in more than one section, and hence prevented priming and interference effects. If an item had appeared as a target in two (or more) sections, even if the subject failed to note the instances, there would be an increase in the familiarity of the word, creating a bias and facilitating memory for the particular stimulus. Conversely, if a distractor had previously appeared as a target, or vice versa, again the item would be more familiar, but because of the change in role of the stimulus, interference may occur. The use of different items for each section of the test also avoided the problem of inter patient variation in the speed of test completion. If recall, paired association, and recognition memory for a given level (Task Familiarisation, Set 1, or Set 2) had been assessed using the same targets for the whole set, with only one initial study phase, the direct comparison of scores across subjects would be of limited value. This is because it would be expected that a subject, who completed the recall and paired association sections of a set more quickly, would attain a higher score on the recognition section, than an individual taking a greater length of time on the preceding tasks. Using different words for each section also prevented non uniform exposure of the stimuli by the final subtests, thus avoiding any bias due to the interaction of primacy and recency effects with priming. Items at the beginning and end of a target series tend to be more readily retained, and this, together with the temporary facilitation of previously presented stimuli, may give rise to individual differences in the saliency of targets.

Following the test structure outlined in Section 2.2.2, words were randomly selected from the item pool to act as targets for each section. The paired association and recognition subtests employed pairs of words, which were constructed purely on the basis of order of selection, hence pair one comprised targets one and two, pair two targets three and four, and so on. There were no purposefully engineered semantically related or unrelated pairings. Any meaningful relationship between the words of a pair

occurred solely by chance. The paired association and recognition sections of the New Test Of Memory also required distractor words, which were randomly chosen from the same pool of items as the targets. In the paired association sections, where the subject was required to choose the correct target word on being given the first item of a pair, the position of this target second word among the distractors was randomly assigned. Likewise, for the recognition test phases, in which the subject was asked to select which of two pairs they had previously seen, the incorrect pairing comprised one target item coupled with a distractor word; which target item should be used in the distractor pair, its position within the pairing, and the order in which the items were displayed on the page were all randomly allocated. For both the paired association and recognition sections, the order in which items were presented in the test phase was decided using randomisation; if the sequence of stimuli presentation was maintained from study to test phase, this occurred purely by chance.

All words were typed in upper case (bold arial font, size 36). For the recall subtests, individual words were displayed centrally on 153mm x 102mm white cards. For the presentation of target pairs in the paired association and recognition sections, the pairs were again positioned centrally, on plain white paper, 297mm x 210mm. The words were well spaced, with approximately 70mm between the two items, the exact distance varied. The spacing for the stimuli of the paired association and recognition test phases followed the format outlined in Figures 2.2.2 and 2.2.3 respectively. A full size reproduction, as an example, and a complete list of the actual stimuli used can be found in Appendices A, B, and C.

Figure 2.2.2: Positioning Of Items For The Verbal Paired Association Test Phases

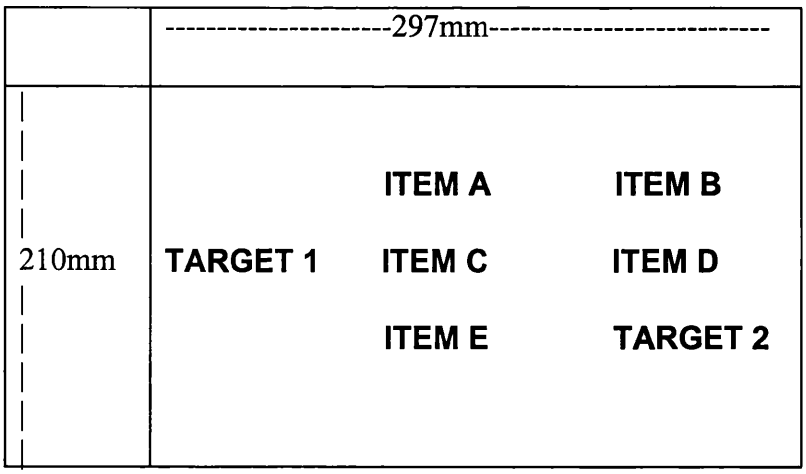
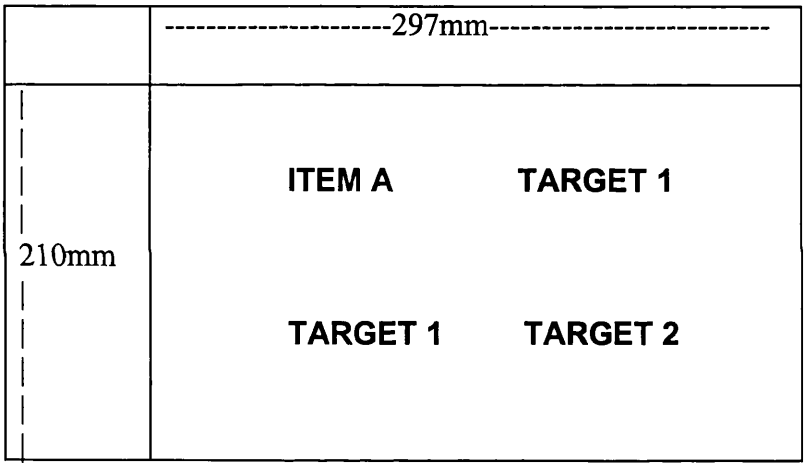


Figure 2.2.3: Positioning Of Items For The Verbal Recognition Test Phases



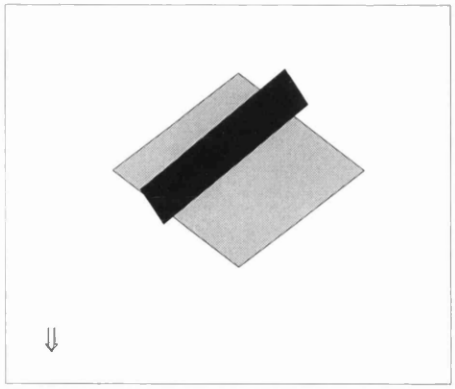
The target stimuli for all verbal sections, at the Task Familiarisation stage, and the two difficulty levels, were presented to the subject for three seconds, during which he or she was asked to make a decision about the word(s) presented, namely, "is this a word you would use every day?" or "are these words you would use every day?". This ensured that the subject had attended to the items, an essential staging post to memory. The presentation rate was maintained by using a hand held stopwatch. In the recall test phases, the subject was simply required to recall as many words as possible, in any order. For the paired association sections, the subject was asked to select, from the six choices, the word they considered had been paired with the item on the left of the page,

the first word of the target pair. In the recognition test phases, the subject was required to choose which of the two pairs of words they had seen previously. Both the paired association and recognition sections allowed the subject to either point or speak their answers. The verbatim instructions used when administering the test can be found in Appendix D.

2.2.4 Spatial Sections:

All spatial stimuli were developed using Corel Draw 6.0 (Corel Corporation, 1988-1995), a graphics package which runs through Windows '95. For the recall sections, the stimuli comprised a filled, regular object, for example, a triangle or rectangle, on which was superimposed a black bar. The bar measured 155mm x 10mm, and was positioned on a given shape by plotting two sets (horizontal reference, vertical reference) of randomly generated co-ordinates, on computerised 50 square x 50 square graph paper. These co-ordinates allowed a line to be drawn, which could then be lengthened or shortened to the required 155mm. Figure 2.2.4 is an example of the recall stimuli. A different fill was used for the background shapes of the Task Familiarisation stage, and Sets 1, and 2 respectively, to minimise interference between the recall sections. A full size reproduction, as an example, and a complete scaled version of the actual stimuli used can be found in Appendices A, B, and C.

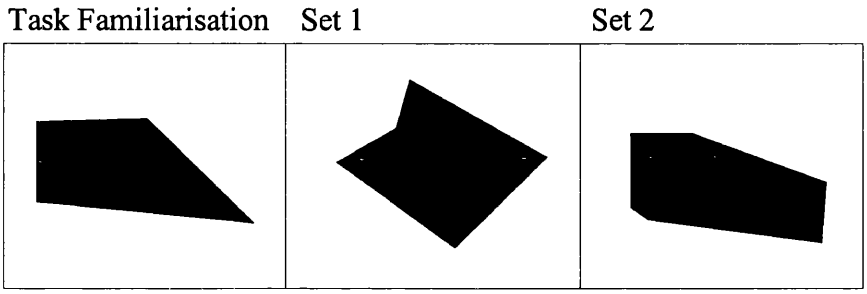
Figure 2.2.4: An Example Of The Recall Stimuli Used In The New Test Of Memory



The stimuli used in the spatial paired association and recognition sections were irregular, black, shapes, which were visually noncomplex and difficult to code verbally. These items were devised by generating a series of random co-ordinates (horizontal reference, vertical reference), plotting them on the computerised 50 square x 50 square graph paper, and linking the points using the Bezier mode (i.e. the co-ordinates were joined by using straight lines) and the rule of least perimeter (i.e. the points were linked together to form the smallest boundary for the shape). For the Task Familiarisation stage, four co-ordinates were randomly generated, with the additional rule that each of these should be located within a different quadrant of the graph paper. This rule was implemented to prevent very small shapes being created, which would be problematic for subjects with poor visual acuity. The stimuli for Set 1 paired association and recognition required five randomly generated co-ordinates, and that for Set 2, six. All shapes were examined by the same, objective observer who ensured that the specified number of points were clearly visible. This confirmed that there was no bias in the saliency of the shapes, that is, if an indistinct co-ordinate placed points along a straight line, it may insinuate that the stimulus item possessed one corner less than others in the Set, and therefore facilitate memory of that particular shape. An example of the items

used in the paired association and recognition sections is shown in Figure 2.2.5. A full size reproduction, as an example, and a complete scaled version of the actual stimuli used can be found in Appendices A, B, and C.

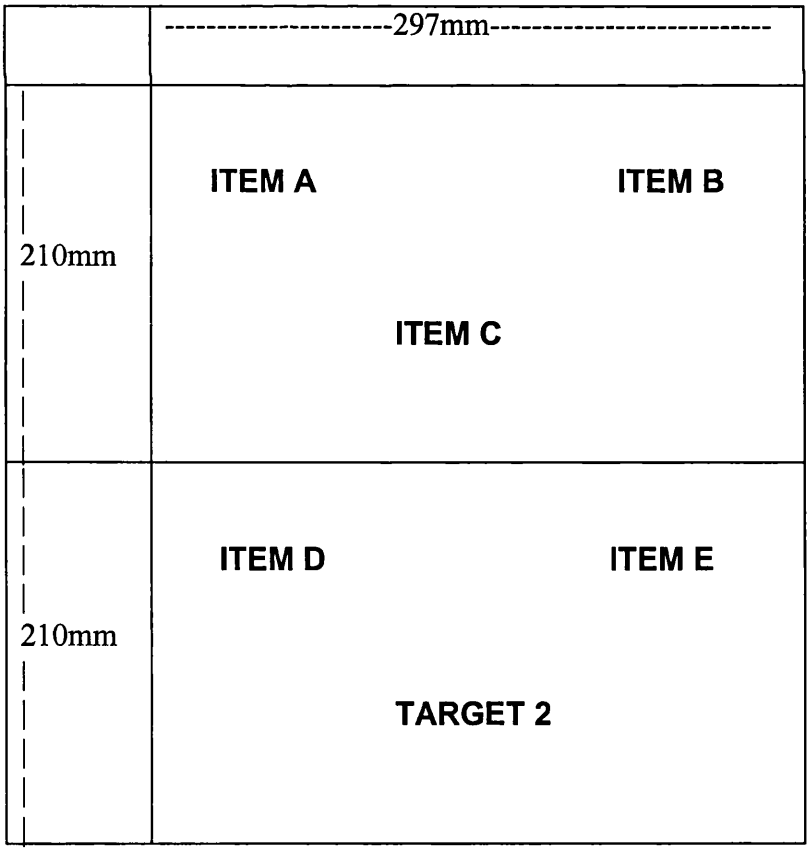
Figure 2.2.5: An Example Of The Paired Association And Recognition Stimuli Used In The New Test Of Memory



The construction of the pairs of shapes employed in the paired association and recognition subtests was based solely on the of order of item development, hence pair one comprised targets one and two, pair two targets three and four, and so on. These sections also required distractor shapes, which were generated using the same method detailed above. In the paired association test sections, where the subject was asked to select the second shape of a target pair, having been given the first, the position of the second target among the distractors was randomly assigned. Likewise, for the recognition test phases, in which the subject selected which of two pairs they had seen previously, the incorrect pairing comprised one target item coupled with a distractor shape; which target item should be used in the distractor pair, its position within the pairing, and the order in which the items were displayed on the page were all randomly allocated. For all spatial sections, the order in which items were presented in the test phase was decided using randomisation; if the sequence of stimuli presentation was maintained from study to test phase, this occurred purely by chance.

All recall target items were positioned centrally on plain white paper, 297mm x 210mm. An additional sheet, with exactly the same dimensions and placement was used for the copying and test phases. For the paired association and recognition sections, the target pairs were displayed horizontally, with approximately 120mm between the items; the exact distance varied. The positioning of the stimuli of the paired association test phases is shown in Figure 2.2.6, with the first of the target pairs being presented centrally on 153mm x 102mm white cards. The placement of the items of the recognition test phases followed the format of the verbal items, previously outlined in Figure 2.2.3.

Figure 2.2.6: Positioning Of Items For The Spatial Paired Association Test Phases (target 1 is to the left of the display)



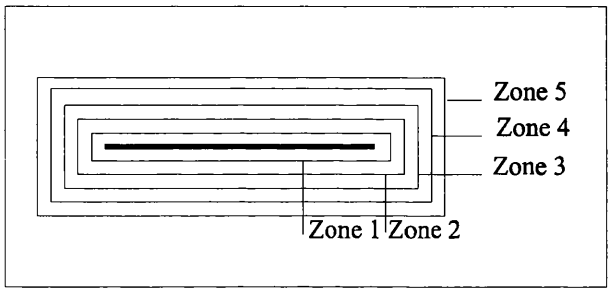
In the spatial recall sections of the Task Familiarisation stage, and Sets 1 and 2, the study phase entailed the subject copying the position of the bar shown in the target

stimulus, having been provided with the background shape and replica bar. The bar used by the subject was made of wood, and measured 155mm x 10mm x 3mm. The target item remained visible during the study period, and the subject was encouraged to perform the task at a reasonable speed. The subject was also informed that recall would subsequently be assessed. In the test phase, the subject was asked to position the bar from memory, once again having been supplied with the background shape and bar. For the Task Familiarisation stage, recall was measured after three target stimuli had been presented. For Set 1, as there were 10 target items, the shapes were copied and tested as a set of three, four, and then three again. Set 2, entailed the copying and recall assessment being conducted with a set of three, two sets of four, and then three again. The verbatim instructions used when administering the test can be found in Appendix D.

Copying and recall memory were scored using a system of concentric zones, 1cm apart, around the exact position of the bar. For each item, the position in which the subject placed the bar was scored from zero to five: a score of five was awarded if the whole of the bar was located within a zone 1cm around the exact position; a score of four was given if the bar was within a zone 2cm around the correct position; and so on up to a maximum zone of 5cm around the exact position, for which the patient was awarded one point (see Figure 2.2.7 for an example of the zones). The number of points allocated for a given item was dependant on the part of the bar in the furthest zone (e.g. if the majority of the bar fell in the zone 3cm from the target position, with one end in the zone 4cm away, two points were awarded, not three). If any part of the bar fell outside the zones, a score of zero was allocated. The correct position of the bar was determined by using an acetate, on to which the target stimulus had been printed, and the zones marked. On examination of the data, scores of three, four or five for each

item, were taken to indicate the correct position of the bar, when allocating the overall scores for the recall sections. This allowed totals comparable to those of the verbal recall sections, hence, Task Familiarisation was out of a maximum of six, for Set 1 the maximum total was 10, and Set 2 was out of 14. This criterion was chosen because, it was noted that if a subject did place the bar correctly, in most cases, the positioning was within 3cm of the exact location.

Figure 2.2.7: An Example Of The Zones Used In The Scoring System



In the paired association and recognition sections, stimuli were presented to the subject for four seconds, during which he or she was asked to make a decision about the pairs, namely, "are these shapes you could easily copy?". This ensured that the subject had attended to the items. As noted in Section 2.2.3 for the verbal stimuli, the rate of presentation was maintained by using a hand held stopwatch. For the paired association sections, the subject was asked to select, from six choices, the shape they considered had been paired with the item presented to the left of the choices, the first shape of the target pair. In the recognition test phases, the subject was required to choose which of the two pairs of stimuli they had seen previously. The verbatim instructions used when administering the test can be found in Appendix D.

The test was always administered in the order Task Familiarisation, Set 1, Set 2, however, whether the verbal or spatial sections of the sets were administered first was

decided by randomisation for each subject. Thus a subject either completed the test in the order: verbal Task Familiarisation, spatial Task Familiarisation, verbal Set 1, spatial Set 1, verbal Set 2, spatial Set 2; or spatial Task Familiarisation, verbal Task Familiarisation, spatial Set 1, verbal Set 1, spatial Set 2, verbal Set 2. Appendices A, B, and C provide a full sized reproduction, as an example, of the stimuli and format for verbal and spatial recall, paired association, and recognition sections, and a scaled version of all the actual test items.

2.2.5 Chance Scores:

The verbal recall sections of the New Test Of Memory require the subject to retrieve items without any prompts, therefore the probability of answering correctly purely by chance is very small. Similarly, in the spatial recall sections, the number of positions of the bar is so great, that the probability of correct placement by chance is negligible, and can be discounted. However, the verbal and spatial paired association and recognition sections employ a multiple choice format, and therefore there is always a calculable probability that the correct answer may be selected by chance. For a single item, the probability of choosing the correct answer by chance can be determined, and as the probability of getting an item correct is independent of whether or not other items are answered correctly, the overall chance score can be easily computed. The chance scores for the paired association and recognition sections, applicable for the verbal and spatial sections, at the Task Familiarisation Stage, and for both levels of difficulty are shown in Table 2.2.1. The calculations, using the binomial method, are given in Appendix E.

Table 2.2.1: The Chance Scores For The Paired Association And Recognition Sections Of The New Test Of Memory, At The Task Familiarisation Stage And For Both Sets.

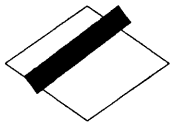
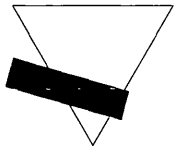
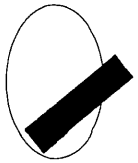
	Task Familiarisation	Set 1 5 items	Set 2 9 items
Paired Association 6 choices per item	0.5	0.83	1.5
Recognition 2 choices per item	1.5	2.5	4.5

2.2.6 Summary:

Table 2.2.2 provides a summary of stimuli and format of the New Test Of Memory

Table 2.2.2: The Format And Examples Of The Stimuli Used In The New Test Of Memory

	Verbal Recall Sections	**Verbal Paired Association Sections**	**Verbal Recognition Sections**
TF	6 individual items e.g. **PEN**	3 pairs of items e.g. **WHEAT - SURPRISE**	3 pairs of items e.g. **DRAW - PIE**
Set 1	10 individual items e.g. **INCREASE**	5 pairs of items e.g. **DAY - ENTRANCE**	5 pairs of items e.g. **PRIDE - BASE**
Set 2	14 individual items e.g. **COURT**	9 pairs of items e.g. **SERIOUS - CLOSE**	9 pairs of items e.g. **MOTOR - NOTICE**

	Spatial Recall Sections	**Spatial Paired Association Sections**	**Spatial Recognition Sections**
TF	6 individual items e.g. 	3 pairs of items e.g. 	3 pairs of items e.g. 
Set 1	10 individual items e.g. 	5 pairs of items e.g. 	5 pairs of items e.g. 
Set 2	14 individual items e.g. 	9 pairs of items e.g. 	9 pairs of items e.g. 

TF = Task Familiarisation

2.3 THE CONTROL SAMPLE: METHOD

2.3.1 Test Battery And Administration Procedures:

The control sample completed the following neuropsychological tests:

1) National Adult Reading Test - Revised (NART-R, Nelson & Willison, 1992). The NART-R comprises 50 words that do not obey English rules of grapheme-phoneme representation and pronunciation. Nelson and McKenna (1975) demonstrated that word reading ability and general intelligence are highly correlated, that word reading ability remains well preserved in dementia, and that it provides an accurate indicator of premorbid general intelligence. The items of the NART-R are all phonetically irregular words, which can only be pronounced correctly if the subject is familiar with them. Therefore, a test in which the subject must read aloud such items provides a very sensitive measure of reading vocabulary, and hence optimum intellectual functioning (Paque & Warrington, 1995). The NART-R was included in the test battery because it provides an accurate estimate of premorbid IQ, which is acquired using a very brief assessment tool.

2) Vocabulary subtest of the Wechsler Adult Intelligence Scale - Revised (WAIS-R, Wechsler, 1981). The vocabulary subtest of the WAIS-R requires the subject to give the meaning of a maximum of 35 words. The subject's responses are recorded verbatim and scored using a two point system. The vocabulary subtest of the WAIS-R was included in the test battery to provide a measure of general verbal ability.

3) Spatial analogy section of the Verbal And Spatial Reasoning Test (VESPAR, Langdon & Warrington, 1995). The spatial analogy subtest of the VESPAR examines this inductive reasoning skill using a set of 25, four alternative multiple choice problems. It provides a relatively pure measure of reasoning ability, by virtue of

minimising the influence of peripheral motor and sensory impairments and reducing the confounding effects of focal cognitive deficits. The spatial analogy section was administered to the control sample to provide a measure of general spatial intelligence.

4) The New Test Of Memory, which has already been detailed in Section 2.2.

Control subjects were also asked to provide the demographic details of: sex, date of birth, ethnic group, marital status, educational level, and current occupation, and to complete the following tests:

5) Hospital Anxiety And Depression Scale (HADS, Zigmond & Snaith, 1983). The HADS is a questionnaire designed to detect anxiety and depression in general medical outpatients. It comprises seven items, rated on a four point scale, relevant to each emotion, which were selected to reduce the effects of physical illness on the measurement of mood disorders.

6) Nine Hole Peg Test (NHPT, Mathiowetz et al., 1985). The NHPT is an assessment of manual dexterity or upper limb function. The subject must pick up individually nine pegs and place them in nine holes, in any order. He or she is then required to remove the pegs, again, one at time, in any order. The task is timed and performance with both the dominant and non dominant hands recorded.

Standardised administration procedures were adopted for all assessments and the order in which the neuropsychological tests were given to the subject was randomised, to minimise the effects of fatigue, practice, or other variables introducing a systematic bias into the results. As with the New Test Of Memory, whether the subject first received the verbal or spatial sections of each set was also randomised. All control subjects were assessed alone, across a desk or table, in a familiar environment, that is, a quiet room either at their home or place of work.

2.3.2 Subjects:

The control sample comprised 85 healthy individuals, who were born and educated in England, and had no history of neurological or significant psychiatric disease. The sample was stratified for sex, age (18-70 years), and NART-R IQ (80-120), and subjects were recruited from a number of companies and organisations in Central and Southern England. Of the control sample, 54 individuals volunteered through their employing organisation, 18 subjects were recruited from Women's Institutes or Social Clubs, nine were spouses or carers of people with MS and four individuals were approached because they had shown an interest in taking part in the study. A list of the institutions participating in the study can be found in Appendix F. All subjects were informed of the nature and purpose of the project prior to testing, and were given a written information sheet, a copy of which can be found in Appendix G. Volunteers gave verbal consent that they were happy to participate in the study and were assured of the confidentiality of the data they were providing.

Four individuals in full time employment who had originally volunteered as control subjects, subsequently declined to take part. This was due to short staffing increasing their work load, such that they could not be spared. Table 2.3.1 details the number of control subjects that completed each part of the battery. One subject did not complete any spatial recall subtests, not even the Task Familiarisation stage, because short staffing meant that time to take part in the study was minimal, and the author considered these sections took a comparatively long time, relative to the number of other tasks which could be completed in the same period. Two individuals declined to complete any section of Set 2 (the more difficult level), as they were anxious to return to their work. A further eight subjects did not complete Set 2 spatial recall, and six of these same volunteers did not complete Set 2 spatial paired association and recognition. In all

these cases subjects declined because time was limited or they expressed fatigue. Inspection of the table showed that the amount of missing data was small, and a Mann-Whitney test with a Bonferroni Correction for multiple tests (Bland & Altman, 1995) failed to find any significant differences between the demographic characteristics or the scores on Task Familiarisation and Set 1 (the easier level), verbal and spatial recall, paired association, and recognition, of those who did and did not go on to complete Set 2. It was unlikely, therefore, that the missing data would have biased the results in a significant manner.

Table 2.3.1: The Number Of Control Subjects Who Completed Each Section Of The Neuropsychological Test Battery

Neuropsychological Test	No. Subjects
NART-R	85
Vocabulary Subtest of WAIS-R	85
Spatial Analogy Section of VESPAR	85
New Test Verbal TF RCLL	85
PA	85
RECOG	85
New Test Verbal Set 1 RCLL	85
PA	85
RECOG	85
New Test Verbal Set 2 RCLL	83
PA	83
RECOG	83
New Test Spatial TF RCLL	84
PA	85
RECOG	85

Neuropsychological Test	No. Subjects
New Test Spatial Set 1 RCLL	84
PA	85
RECOG	85
New Test Spatial Set 2 RCLL	75
PA	77
RECOG	77

TF = Task Familiarisation; RCLL = recall memory; PA = paired association; RECOG = recognition memory

2.4 THE CONTROL SAMPLE: RESULTS

2.4.1 Demographic Characteristics:

The demographic characteristics of the control sample as a whole can be found in Table 2.4.1. Table 2.4.2 shows these features for the control sample divided into three age groups, namely, 18 to 40 years, 41 to 55 years, and 56 to 70 years.

Table 2.4.1: Demographic Characteristics Of The Control Group (N=85)

Sex (Male:Female)	29:56
Age in years: mean (SD)	43.42 (12.39)
median (range)	44.00 (21-67)
Ethnic Group: Caucasian	81
Afro/Caribbean	1
Asian/Asian Pacific	3
Marital Status: Single	28
Married	49
Divorced/Separated	6
Widowed	2
No. of controls with children	52
No. of controls without children	33
Educational Level: no qualifications	17
'O' levels/CSEs/GCSEs	32
'A' levels	12
Degree	24
Current Occupation/Social Class:	
professional	7
managerial & technical	24
skilled occupations	38
partly skilled	0
retired/housewife/ unemployed	16
Dominant Hand: right	76
left	9

NHPT in seconds:	
dominant hand mean (SD)	18.39 (2.52)
median (range)	18.04 (14.37-25.44)
non dominant hand mean (SD)	19.45 (3.04)
median (range)	19.09 (15.03-30.31)
[1]**HADS:** total score mean (SD)	9.92 (4.55)
anxiety score mean (SD)	6.58 (2.91)
depression score mean (SD)	3.33 (2.37)

[1] data based on 83 controls, i.e. 2 individuals missing

Table 2.4.2: Demographic Characteristics Of The Control Group Divided By Age

	Controls aged 18-40 years (N=38)	Controls aged 41-55 years (N=28)	Controls aged 56-70 years (N=19)
Sex (Male:Female)	12:26	10:18	7:12
Age in years: mean (SD)	31.89 (5.46)	47.32 (3.42)	60.74 (4.15)
median (range)	33.50 (21-40)	47.00 (42-55)	62.00 (56-67)
Ethnic Group:			
Caucasian	34	28	19
Afro/Caribbean	1	0	0
Asian/Asian Pacific	3	0	0
Marital Status:			
Single	24	3	1
Married	13	22	14
Divorced/Separated	1	3	2
Widowed	0	0	2
No. of controls with children	10	26	16
No. of controls without children	28	2	3
Educational Level:			
no qualifications	2	6	9
'O' levels/CSEs/GCSEs	14	14	4
'A' levels	5	4	3
Degree	17	4	3

	Controls aged 18-40 years (N=38)	Controls aged 41-55 years (N=28)	Controls aged 56-70 years (N=19)
Current Occupation /Social Class:			
professional	5	2	0
managerial & technical	12	9	3
skilled occupations	20	11	7
partly skilled	0	0	0
retired/housewife/unemployed	1	6	9
Dominant Hand: right	34	26	16
left	4	2	3
NHPT in seconds:			
dominant hand mean (SD)	17.75 (2.22)	18.15 (1.99)	20.03 (3.14)
median	17.76	17.97	19.70
(range)	(14.37-23.20)	(15.09- 23.09)	(16.10-25.44)
non dominant hand mean (SD)	18.49 (2.12)	19.23 (1.90)	21.71 (4.61)
median	18.27	19.21	19.51
(range)	(15.03- 24.61)	(16.38- 22.36)	(16.29-30.31)
HADS:			
total score mean (SD)	10.89 (4.55)	9.92 (4.77)[1]	7.95 (3.73)
anxiety score mean (SD)	7.37 (2.85)	6.12 (2.76)[1]	5.63 (2.95)
depression score mean (SD)	3.50 (2.39)	3.81 (2.62)[1]	2.32 (1.67)

[1] data based on 26 controls, i.e. 2 individuals missing

A chi-square test demonstrated that overall there was a significantly greater number of women in the control sample ($\chi^2 = 8.576$; df = 1; p = 0.003), however, this bias did not vary significantly when the sample was divided into the three age groups ($\chi^2 = 0.203$; df = 2; p = 0.903). The higher frequency of female controls only reached significance in the age group 18 to 40 years ($\chi^2 = 5.158$; df = 1; p = 0.023), where spanning the NART-R IQ range was considered the main priority in recruiting the

sample. The distribution of sex by current occupation/social class was not significantly different, if the preponderance of female volunteers was taken into account ($\chi^2 = 7.941$; df = 2; p = 0.085).

2.4.2 Performance On Neuropsychological Tests:

Performance on the established neuropsychological assessments included in the cognitive test battery for the control subjects are shown in Tables 2.4.3 and 2.4.4 (raw scores are detailed in Appendix H). The mean (SD) full scale IQ using the NART-R, for the whole group, was 103.22 (10.17), and 100.24 (9.27), 103.71 (10.82), and 108.47 (9.06), for the three age groups, respectively. A sample mean slightly above 100 is a consistent finding in control groups at this and other metropolitan centres, for example, Nelson and Willison (1992) reported a full scale mean IQ of 107.4. This is thought to reflect an urban population, which typically comprises a higher proportion of professional as opposed to unskilled workers.

When comparing the mean scores of the three age groups of controls on the neuropsychological tasks, the only significant difference was found between the mean NART-R IQ of the controls aged 18-40 years and that of the controls aged 56-70 years. In healthy individuals, the effects of intelligence on memory may be less pronounced than those of ageing (Walton & Black, 1957; Newcombe & Steinberg, 1964; Bornstein & Chelune, 1988; Ruff et al., 1988), therefore it is unlikely that this finding will impact significantly on the age group scores recorded using the New Test Of Memory.

Tables 2.4.3 and 2.4.4 also detail the 95% confidence limits around the mean values attained by the controls, on each of the neuropsychological tasks administered. It can be seen that in the majority of cases these limits are close to the mean, suggesting

accuracy, and indicating that the control sample is a relatively reliable estimate of the performance of the general, healthy population. Raw scores on the neuropsychological tasks can be found in Appendix H.

Table 2.4.3: Mean, Standard Deviation, And 95% Confidence Intervals For The Cognitive Scores Of The Control Group (N=85)

NART-R:	
full scale IQ mean (SD)	103.22 (10.17)
median (range)	103.00 (80-120)
95% confidence limits	101.01-105.42
WAIS-R: vocabulary subtest	
scaled score mean (SD)	9.26 (2.13)
median (range)	9.00 (6-15)
95% confidence limits	8.80-9.72
VESPAR: spatial analogy section	
equivalent IQ mean (SD)	105.59 (5.88)
median (range)	106.00 (90-117)
95% confidence limits	104.32-106.86

Table 2.4.4: Mean, Standard Deviation, And 95% confidence Intervals For The Cognitive Scores Of The Control Group (Divided By Age)

	Controls aged 18-40 years (N=38)	Controls aged 41-55 years (N=28)	Controls aged 56-70 years (N=19)
NART-R:			
full scale IQ mean (SD)	100.24 (9.27)	103.71 (10.82)	108.47 (9.06)
median (range)	100.50 (80-120)	104.00 (70-120)	110.00 (81-120)
95% confidence limits	97.20-103.28	99.51-107.91	104.10-112.84
WAIS-R:			
vocabulary subtest			
scaled score mean (SD)	9.00 (1.80)	9.25 (2.37)	9.79 (2.39)
median (range)	9.00 (6-14)	8.00 (7-15)	10.00 (6-15)
95% confidence limits	8.41-9.59	8.33-10.17	8.64-10.94
VESPAR:			
spatial analogy section			
equivalent IQ mean (SD)	104.89 (5.97)	104.86 (5.76)	108.05 (5.50)
median (range)	106.00 (90-116)	105.00 (91-115)	108.00 (96-117)
95% confidence limits	102.93-106.85	102.63-107.09	105.40-110.70

2.4.3 Distribution Of IQ:

To ascertain whether intelligence was normally distributed across the entire age range of the control sample, frequency distributions of NART-R full scale IQ were constructed for each age group (Figures 2.4.1, 2.4.2, 2.4.3). Skewness and kurtosis calculations were used as tests of normality. (If the ratio of skewness or kurtosis to its respective standard error is less than -2 or greater than +2 normality is rejected. With regard to skewness, a larger positive value indicates the distribution is shifted to the left; a larger negative value, that the distribution is shifted to the right. With regard to kurtosis, a larger positive value indicates that the tails of the distribution are longer than

those of a normal distribution; a larger negative value indicates short tails, suggestive of a box-shaped uniform distribution). The age groups 18 to 40 years and 41 to 55 years were found to follow a normal distribution, as can be seen in Figures 2.4.1 and 2.4.2. However, for the age group 56 to 70 years, the distribution was skewed to the right, towards high IQ, with longer tails than normal (skewness = -2.98; kurtosis = 3.76). This is unexpected, given the higher mean NART-R IQ recorded for this age group. The implications of the finding have been discussed in Section 2.4.2.

Figure 2.4.1: Distribution Of NART-R IQ For The Controls Aged 18 To 40 Years (N=38)

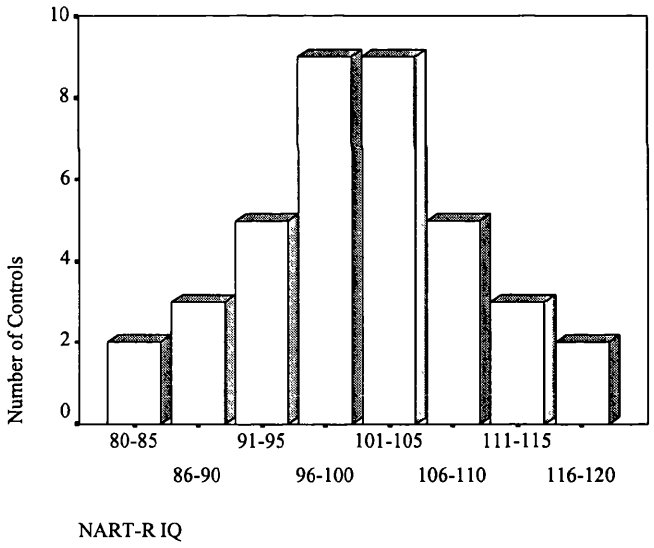


Figure 2.4.2: Distribution Of NART-R IQ For The Controls Aged 41 To 55 Years (N=28)

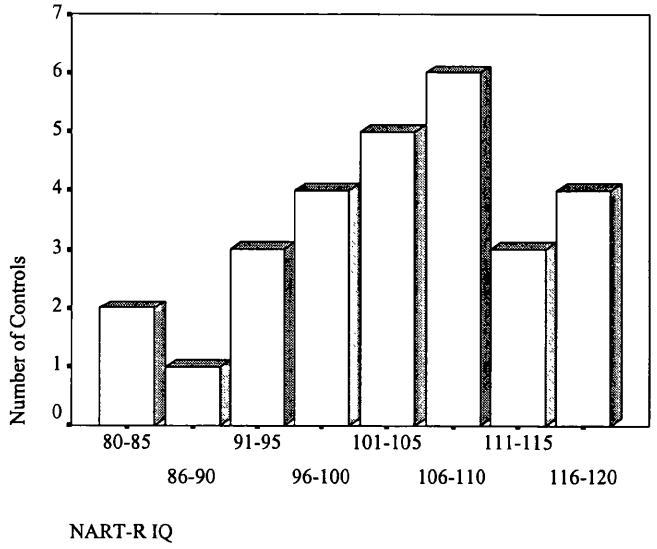
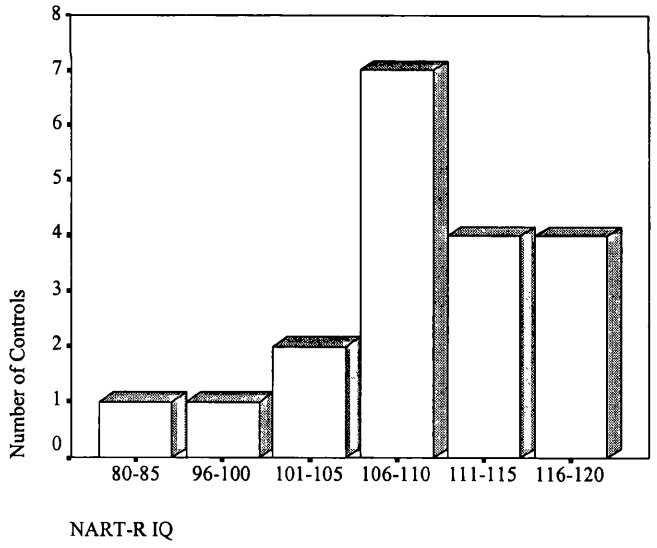


Figure 2.4.3: Distribution Of NART-R IQ For The Controls Aged 56 To 70 Years (N=19)



2.4.4 New Test Of Memory:

As previously detailed in Section 2.2, the New Test Of Memory examines recall memory (RCLL), paired association (PA), and recognition memory (RECOG) at the Task Familiarisation stage, and at two levels of difficulty, for both verbal and spatial domains. The verbal and spatial, Task Familiarisation recall sections, both have a

maximum score of six, while the paired association and recognition subtests are each out of three. The maximum score on the verbal and spatial recall sections of Set 1 (the easier level) is 10 respectively, while for the paired association and recognition subtests, it is five in each case. The verbal and spatial recall subtests of Set 2 (the more difficult level) are both out of 14, with a maximum score of nine on the paired association and recognition sections respectively. The composite totals for each memory domain are the sum of performance at the Task Familiarisation stage, together with that of both Sets 1 and 2.

Table 2.4.5 details the scores of the control group on each section of the New Test Of Memory, while Tables 2.4.6 and 2.4.7 show the composite scores on the verbal and spatial recall, paired association, and recognition sections, and both verbal and spatial sections at the Task Familiarisation stage and Sets 1 and 2, for the three age groups, respectively. Tables 2.4.6 and 2.4.7 also detail the 95% confidence limits around the mean values, and again the intervals are small in the majority of cases, suggesting accuracy, and indicating that the control sample provides a reliable estimate of the performance of the general, healthy population.

Table 2.4.5: Raw Scores For The Control Group (N=85) On The New Test Of Memory

Verbal Memory TF:	
RCLL mean (SD)	4.88 (0.91)
median (range)	5.00 (2-6)
PA mean (SD)	2.60 (0.66)
median (range)	3.00 (1-3)
RECOG mean (SD)	2.86 (0.38)
median (range)	3.00 (1-3)
Verbal Memory Set 1:	
RCLL mean (SD)	5.04 (1.55)
median (range)	5.00 (2-9)
PA mean (SD)	4.00 (0.95)
median (range)	4.00 (2-5)
RECOG mean (SD)	4.72 (0.59)
median (range)	5.00 (2-5)
[1]**Verbal Memory Set 2:**	
RCLL mean (SD)	7.18 (2.27)
median (range)	7.00 (3-12)
PA mean (SD)	6.92 (2.04)
median (range)	8.00 (1-9)
RECOG mean (SD)	8.34 (0.95)
median (range)	9.00 (5-9)

Spatial Memory TF:	
RCLL mean (SD)	3.68 (1.44)[2]
median (range)	4.00 (0-6)[2]
PA mean (SD)	1.28 (0.85)
median (range)	1.00 (0-3)
RECOG mean (SD)	2.36 (0.69)
median (range)	2.00 (0-3)
Spatial Memory Set 1:	
RCLL mean (SD)	4.01 (1.75)[2]
median (range)	4.00 (0-7)[2]
PA mean (SD)	2.21 (1.19)
median (range)	2.00 (0-5)
RECOG mean (SD)	3.05 (1.10)
median (range)	3.00 (0-5)
Spatial Memory Set 2:	
RCLL mean (SD)	5.47 (2.73)[3]
median (range)	5.00 (0-11)[3]
PA mean (SD)	2.75 (1.54)[4]
median (range)	3.00 (0-7)[4]
RECOG mean (SD)	5.43 (1.64)[4]
median (range)	6.00 (2-9)[4]

TF = Task Familiarisation; RCLL = recall memory; PA = paired association; RECOG = recognition memory

[1] based on 83 controls, i.e. 2 individuals missing; [2] based on 84 controls, i.e. 1 individual missing; [3] based on 75 controls, i.e. 10 individuals missing; [4] based on 77 controls, i.e. 8 individuals missing

Table 2.4.6: Mean, Standard Deviation, And 95% Confidence Intervals For The Composite Scores On The Verbal And Spatial Memory Domains Of The New Test Of Memory, For The Controls (Divided By Age)

	Controls age 18-40 years (N=38)	Controls age 41-55 years (N=28)	Controls age 56-70 years (N=19)
Mean (SD) New Test **verbal RCLL total**	18.68 (2.93)[1]	15.75 (3.26)	16.33 (4.39)[5]
95% confidence limits	17.70-19.66	14.49-17.01	14.15-18.51
Mean (SD) New Test **verbal PA total**	14.35 (2.65)[1]	13.25 (2.74)	12.39 (2.03)[5]
95% confidence limits	13.47-15.23	12.19-14.31	11.38-13.40
Mean (SD) New Test **verbal RECOG total**	16.14 (1.38)[1]	15.71 (1.54)	15.83 (1.34)[5]
95% confidence limits	15.68-16.60	15.11-16.31	15.16-16.50
Mean (SD) New Test **verbal total**	49.16 (5.50)[1]	44.71 (5.78)	44.56 (6.64)[5]
95% confidence limits	47.32-51.00	42.47-46.95	41.26-47.86
Mean (SD) New Test **spatial RCLL total**	14.51 (5.14)[2]	12.80 (4.23)[3]	11.27 (4.06)[6]
95% confidence limits	12.75-16.27	11.05-14.55	9.02-13.52
Mean (SD) New Test **spatial PA total**	6.97 (2.22)[2]	6.38 (2.79)[4]	4.88 (2.13)[7]
95% confidence limits	6.21-7.73	5.25-7.51	3.75-6.01
Mean (SD) New Test **spatial RECOG total**	11.69 (2.30)[2]	10.12 (2.32)[4]	10.56 (2.53)[7]
95% confidence limits	10.90-12.48	9.18-11.06	9.21-11.91
Mean (SD) New Test **spatial total**	33.17 (7.27)[2]	29.56 (5.42)[3]	27.00 (7.39)[6]
95% confidence limits	30.67-35.67	27.32-31.80	22.91-31.09

RCLL = recall memory; PA = paired association; RECOG = recognition memory

[1] data based on 37 controls, i.e. 1 individual missing; [2] data based on 35 controls, i.e. 3 individuals missing; [3] data based on 25 controls, i.e. 3 individuals missing; [4] data based on 26 controls, i.e. 2 individuals missing; [5] data based on 18 controls, i.e. 1 individual missing; [6] data based on 15 controls, i.e. 4 individuals missing; [7] data based on 16 controls, i.e. 3 individuals missing

Table 2.4.7: Mean, Standard Deviation, And 95% Confidence Intervals For The Composite Scores, At The Verbal And Spatial Task Familiarisation Stage And The Two Levels Of Difficulty, Of The New Test Of Memory For The Controls (Divided By Age)

	Controls age 18-40 years (N=38)	Controls age 41-55 years (N=28)	Controls age 56-70 years (N=19)
Mean (SD) New Test **verbal total TF**	10.71 (1.23)	10.14 (1.41)	9.89 (1.49)
95% confidence limits	10.31-11.11	9.59-10.69	9.17-10.61
Mean (SD) New Test **verbal total Set 1**	14.21 (1.99)	13.64 (1.85)	13.00 (2.47)
95% confidence limits	13.56-14.86	12.92-14.36	11.81-14.19
Mean (SD) New Test **verbal total Set 2**	24.14 (3.58)[1]	20.93 (3.93)	21.28 (4.73)[5]
95% confidence limits	22.95-25.33	19.41-22.45	18.93-23.63
Mean (SD) New Test **spatial total TF**	7.76 (1.94)	7.44 (1.83)[3]	6.32 (1.63)
95% confidence limits	7.12-8.40	6.72-7.16	5.53-7.11
Mean (SD) New Test **spatial total Set 1**	10.29 (2.79)	8.85 (2.61)[3]	7.95 (2.57)
95% confidence limits	9.38-11.20	7.82-9.88	6.71-9.19
Mean (SD) New Test **spatial total Set 2**	15.09 (4.53)[2]	12.88 (2.73)[4]	12.00 (4.29)[6]
95% confidence limits	13.53-16.65	11.75-14.01	9.62-14.38
Mean (SD) New Test **overall total**	82.46 (10.49)[2]	74.92 (9.37)[4]	71.60 (12.83)[6]
95% confidence limits	78.86-86.06	71.05-78.79	64.49-78.71

TF = Task Familiarisation

[1] data based on 37 controls, i.e. 1 individual missing; [2] data based on 35 controls, i.e. 3 individuals missing; [3] data based on 27 controls, i.e. 1 individual missing; [4] data based on 25 controls, i.e. 3 individuals missing; [5] data based on 18 controls, i.e. 1 individual missing; [6] data based on 15 controls, i.e. 4 individuals missing

Inspection of the descriptive raw scores for each age group showed that the new test demonstrates the expected age effects of a memory assessment, that is, that memory function declines with age (Warrington, 1984; Baddeley, 1999). Warrington (1984) demonstrated a decrease, with age, in recognition memory capabilities, using a test of both words and faces. Similarly, Baddeley (1999) reported that recall and recognition memory of verbal and visuo-spatial stimuli are influenced by age, a contributory factor being inaccuracies in encoding by older individuals.

Age was found to correlate significantly, in a negative direction, with both the verbal and spatial totals, and the overall total of the New Test Of Memory (Table 2.4.8). NART-R IQ correlated significantly, but positively, with the verbal and spatial total scores, and the overall total, while sex only correlated with the spatial sections. The direction of this correlation was negative; males were coded with "1" and females with "2". This correlation is unsurprising, given that superior spatial visualisation and orientation skills have been reported in males, relative to females (McGee, 1979).

Table 2.4.8: A Correlation Matrix Of The Relationship Between Age, Sex, And NART-R IQ For The Control Group

	Age	Sex	NART-R IQ	New Test Verbal Total	New Test Spatial Total	New Test Overall Total
Age						
Sex	-0.08					
NART-R IQ	0.39 ***	-0.12				
New Test Verbal Total	-0.33 **	0.05	0.29 **			
New Test Spatial Total	-0.32 **	-0.31 **	0.25 *	0.48 ***		
New Test Overall Total	-0.36 ***	-0.19	0.35 **	0.85 ***	0.86 ***	

Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Tables 2.4.9 and 2.4.10 detail the correlations between NART-R IQ and verbal and spatial performance at the Task Familiarisation stage, and at the two levels of difficulty of the New Test Of Memory, respectively. It can be seen that level of intelligence does not have a significant impact on ability to learn the actual verbal and spatial tasks which comprise the new measure, that is, the Task Familiarisation stage, but does affect declarative memory performance, which is assessed by Sets 1 and 2.

Table 2.4.9: A Correlation Matrix Of The Relationship Between NART-R IQ And Verbal Sections Of The New Test Of Memory, At The Task Familiarisation Stage And Two Difficulty Levels, For The Control Group

	NART-R IQ	New Test TF Verbal Total	New Test Set 1 Verbal Total	New Test Set 2 Verbal Total
NART-R IQ				
New Test TF Verbal Total	0.19			
New Test Set 1 Verbal Total	0.23 *	0.31 **		
New Test Set 2 Verbal Total	0.25 *	0.41 ***	0.48 ***	

TF = Task Familiarisation
Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Table 2.4.10: A Correlation Matrix Of The Relationship Between NART-R IQ And Spatial Sections Of The New Test Of Memory, At The Task Familiarisation Stage And Two Difficulty Levels, For The Control Group

	NART-R IQ	New Test TF Spatial Total	New Test Set 1 Spatial Total	New Test Set 2 Spatial Total
NART-R IQ				
New Test TF Spatial Total	0.17			
New Test Set 1 Spatial Total	0.21 *	0.32 **		
New Test Set 2 Spatial Total	0.17	0.36 ***	0.53 ***	

TF = Task Familiarisation
Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

2.4.5 Reliability:

The reliability of a measure refers to its consistency, reproducibility, and stability (Bryman & Cramer, 1990). External reliability (i.e. test-retest reliability) was not assessed in the current study. Internal reliability examines the extent to which items comprising the assessment tool measure the same concept (Hobart et al., 1996). It is assessed using Cronbach's Alpha (Cronbach, 1951), which is the average of all possible split-half reliability coefficients (Kline, 1993). For the control group, the Cronbach's Alpha of the verbal sections of the New Test Of Memory was 0.76, and that of the spatial sections 0.75. These show the assessment to be a reliable, homogeneous measure.

Tables 2.4.11 and 2.4.12 refer to the internal consistency of the New Test Of Memory. Table 2.4.11 is the correlation matrix of verbal recall, paired association, and recognition, and spatial recall, paired association, and recognition sections, while Table 2.4.12 is the correlation coefficients of Task Familiarisation and the two Sets, for both verbal and spatial sections. The strength of the correlations are as expected for a measure which was designed to assess a variety of different types of memory, and cover a wide range of abilities. This is because the various memory domains possess a degree of general or non-specific memory competency.

2.4.6 Validity:

Validity can be described as the extent to which a measure assesses the concept it purports or is intended to measure (Bryman & Cramer, 1990). Face validity is concerned with rapport and public relations, and pertains to whether a test 'looks valid' to the target population, that is, that it apparently reflects the content of the concept to

be assessed (Bryman & Cramer, 1990). Informal feedback from the control sample would suggest that the New Test Of Memory possessed face validity, as all subjects considered it to measure memory, with no spontaneously reported criticisms of irrelevant or inappropriate format or items.

The construct validity of a test is the extent to which the assessment may be considered to measure the hypothetical quality, trait, or construct it was designed to measure (Streiner & Norman, 1989). Table 2.4.13 details the Spearman's Rank Correlation Coefficients of verbal and spatial total scores of the New Test Of Memory, with the neuropsychological tasks assessing general verbal and spatial skills, completed by the control subjects. It can be seen that these correlations are significant, suggesting that the tasks share 'g', but, as expected they are moderate. (The general or 'g' factor was introduced by Spearman (1904; 1927), and refers to the single, common factor which all intellectual activities share.) The vocabulary subtest of the WAIS-R and the spatial analogy section of the VESPAR, assess language and spatial reasoning, not memory specifically, thus it would be surprising if the correlations were very strong.

Table 2.4.11: A Correlation Matrix Of The Verbal And Spatial Sections Of The New Test Of Memory, For The Control Group

	Verbal RCLL total	Verbal PA total	Verbal RECOG total	Verbal total	Spatial RCLL total	Spatial PA total	Spatial RECOG total	Spatial total
Verbal RCLL total								
Verbal PA total	0.52 ***							
Verbal RECOG total	0.31 **	0.37 ***						
Verbal total	0.87 ***	0.81 ***	0.54 ***					
Spatial RCLL total	0.45 ***	0.27 *	0.25 *	0.44 ***				
Spatial PA total	0.31 **	0.25 *	-0.07	0.28 *	0.25 *			
Spatial RECOG total	0.37 ***	0.16	0.19	0.34 **	0.38 ***	0.16		
Spatial total	0.52 ***	0.30 **	0.17	0.48 ***	0.88 ***	0.56 ***	0.60 ***	

RCLL = recall memory; PA = paired association; RECOG = recognition memory
Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Table 2.4.12: A Correlation Matrix Of The Task Familiarisation Stage And The Two Levels Of Difficulty Of The New Test Of Memory, For The Control Group

	Verbal Total TF	Verbal Total Set 1	Verbal Total Set 2	Verbal Total	Spatial Total TF	Spatial Total Set 1	Spatial Total Set 2	Spatial Total
Verbal Total TF								
Verbal Total Set 1	0.31 **							
Verbal Total Set 2	0.41 ***	0.48 ***						
Verbal Total	0.56 ***	0.71 ***	0.93 ***					
Spatial Total TF	0.28 **	0.28 **	0.32 **	0.38 ***				
Spatial Total Set 1	0.37 ***	0.31 **	0.50 ***	0.53 ***	0.32 **			
Spatial Total Set 2	0.29 **	0.16	0.23 *	0.31 **	0.36 ***	0.53 ***		
Spatial Total	0.39 ***	0.31 **	0.39 ***	0.48 ***	0.59 ***	0.76 ***	0.90 ***	

TF = Task Familiarisation; Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Table 2.4.13: A Correlation Matrix Of The New Test Of Memory With The WAIS-R Vocabulary Subtest And The VESPAR Spatial Analogy Section, For The Control Group

	New Test Verbal total	New Test Spatial total	New Test Overall Total	WAIS-R Vocab.	VESPAR Spatial Analogy
New Test Verbal total					
New Test Spatial total	0.48 ***				
New Test Overall Total	0.85 ***	0.86 ***			
WAIS-R Vocab.	0.38 ***	0.32 **	0.43 ***		
VESPAR Spatial Analogy	0.30 **	0.45 ***	0.43 ***	0.51 ***	

Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Factorial validity is a form of construct validity which uses factor analysis in order to ascertain whether the measure examines the required qualities (Anastasi, 1976). Following convention (Delis et al., 1987; Wechsler, 1987; Compton et al.,1992), composite scores, rather than individual item scores were entered as variables. Tables 2.4.14 and 2.4.15 give details of the two factor solutions for the control data, using principal component analyses with varimax rotation; firstly, when assessing the verbal and spatial recall, paired association, and recognition sections, and secondly, examining

the Task Familiarisation, and two levels of difficulty. It can be seen that the solutions identify strong verbal and spatial components.

Table 2.4.14: Factor Analysis Of The Components Of The New Test Of Memory, Divided By Memory Domains, For The Control Group

Factor 1	**Verbal RECOG** 0.86
	Verbal PA 0.77
	Verbal RCLL 0.63
Factor 2	**Spatial PA** 0.77
	Spatial RCLL 0.64
	Spatial RECOG 0.57

RCLL = recall memory; PA = paired association; RECOG = recognition memory

Table 2.4.15: Factor Analysis Of The Components Of The New Test Of Memory, Divided By Task Familiarisation And Difficulty Level, For The Control Group

Factor 1	**Set 1 Verbal Total** 0.81
	Set 2 Verbal Total 0.80
	TF Verbal Total 0.68
Factor 2	**Set 2 Spatial Total** 0.89
	TF Spatial Total 0.67
	Set 1 Spatial Total 0.65

TF = Task Familiarisation

2.4.7 Range Of Scores:

To determine whether the different sections of the New Test Of Memory graded the range of memory capabilities across the urban adult sample, cumulative frequency distributions for the verbal and spatial recall, paired association, and recognition sections, and the verbal and spatial totals for the Task Familiarisation, and levels of difficulty of the New Test Of Memory, were created (Figures 2.4.4 to 2.4.18). It can be seen that for the verbal and spatial recall, paired association, and recognition sections

the scores do appear to span and grade the ability spectrum. The skewness and kurtosis values for these sections were within the limits set for a normal distribution, with the exception of verbal paired association (skewness -3.60), and verbal recognition (skewness -7.42; kurtosis 8.71), which were skewed to the right. Likewise for verbal and spatial sections at the Task Familiarisation stage, Sets 1 and 2, and the overall total; these all followed a normal distribution apart from Task Familiarisation verbal total (skewness -3.53), which is the training section for words. The multiple choice format for the verbal and spatial paired association, and recognition sections, creates the opportunity to score correctly by chance, and this is reflected by the cumulative frequency distributions.

Figure 2.4.4: A Cumulative Frequency Distribution For The Verbal Recall Total Of The New Test Of Memory, For The Control Group

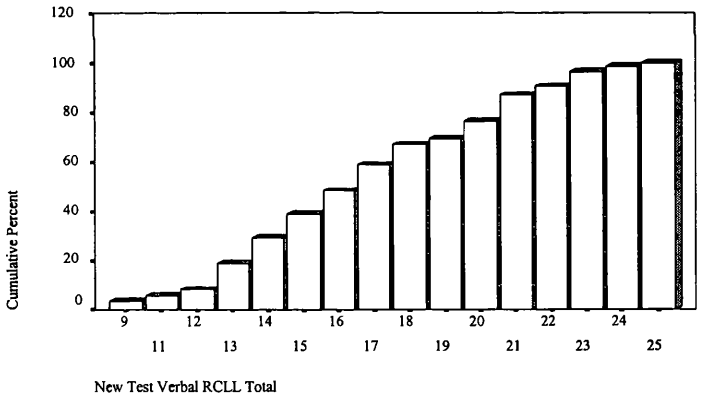


Figure 2.4.5: A Cumulative Frequency Distribution For The Verbal Paired Association Total Of The New Test Of Memory, For The Control Group

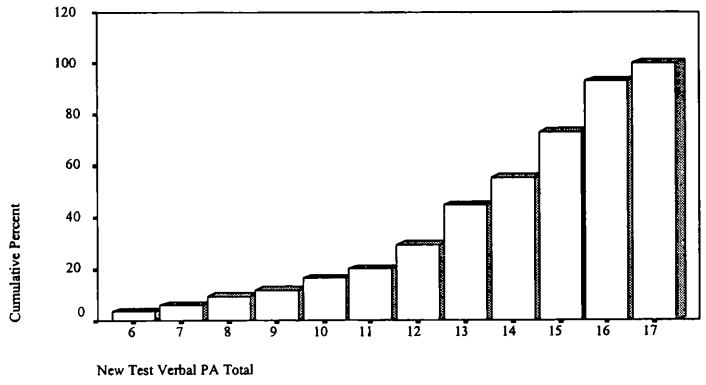


Figure 2.4.6: A Cumulative Frequency Distribution For The Verbal Recognition Total Of The New Test Of Memory, For The Control Group

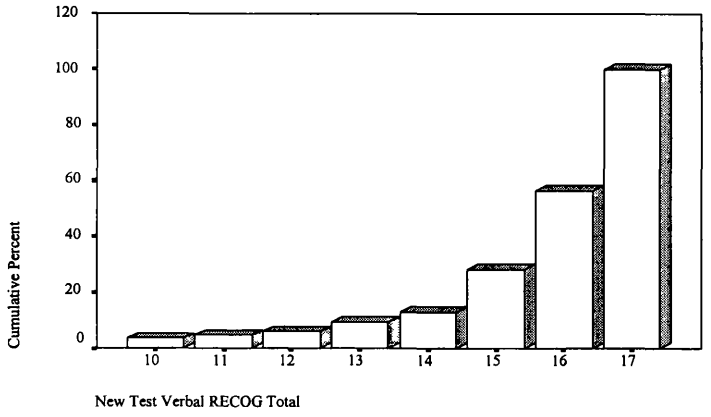


Figure 2.4.7: A Cumulative Frequency Distribution For The Composite Verbal Total Of The New Test Of Memory, For The Control Group

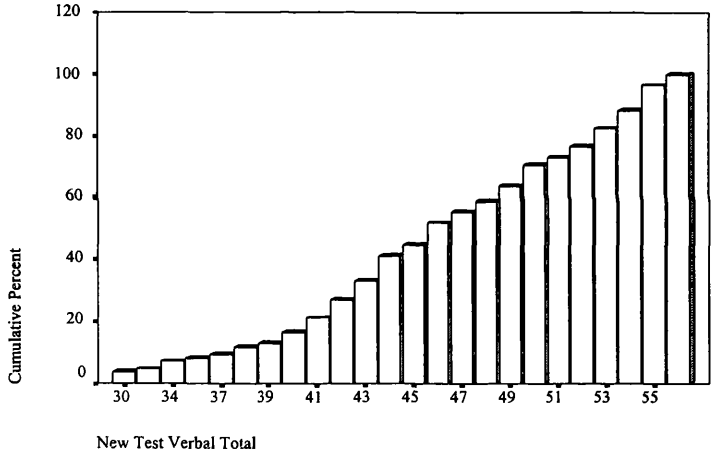


Figure 2.4.8: A Cumulative Frequency Distribution For The Spatial Recall Total Of The New Test Of Memory, For The Control Group

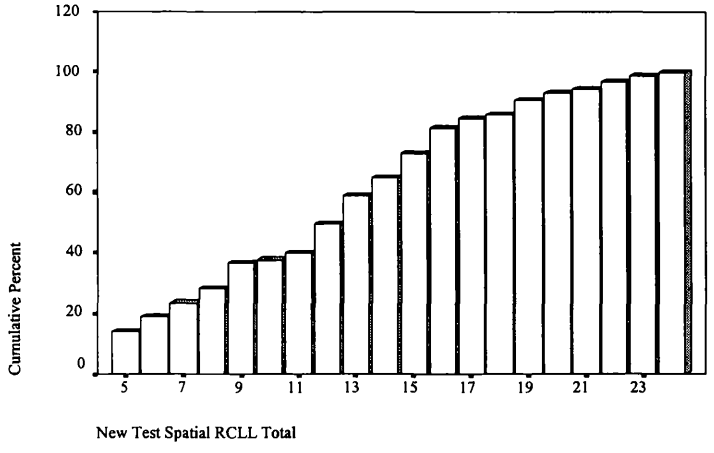


Figure 2.4.9: A Cumulative Frequency Distribution For The Spatial Paired Association Total Of The New Test Of Memory, For The Control Group

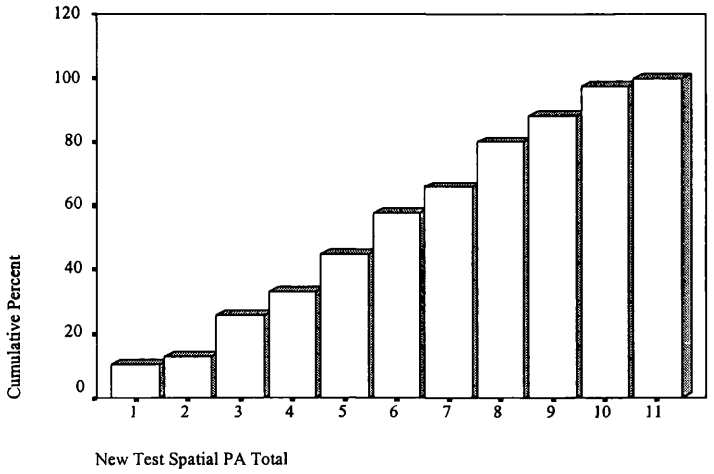


Figure 2.4.10: A Cumulative Frequency Distribution For The Spatial Recognition Total Of The New Test Of Memory, For The Control Group

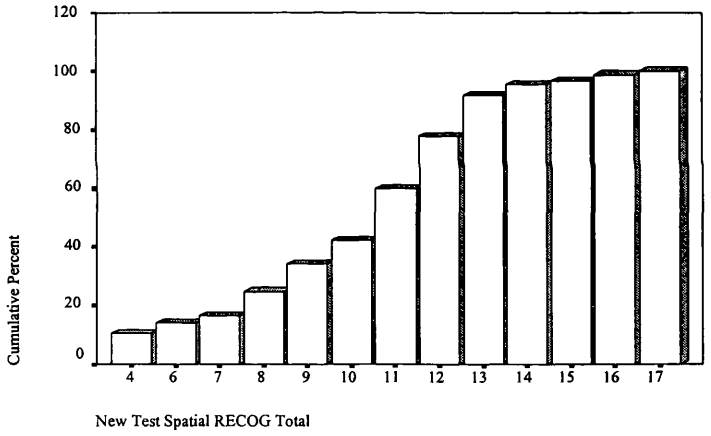


Figure 2.4.11: A Cumulative Frequency Distribution For The Composite Spatial Total Of The New Test Of Memory, For The Control Group

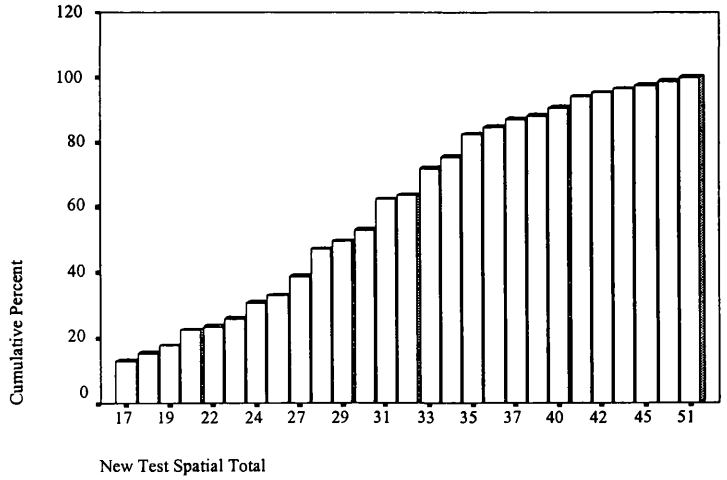


Figure 2.4.12: A Cumulative Frequency Distribution For The Verbal Total Of The New Test Of Memory, At The Task Familiarisation Stage, For The Control Group

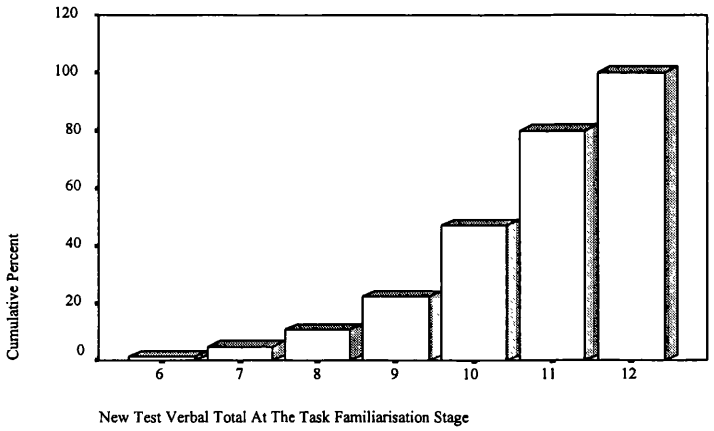


Figure 2.4.13: A Cumulative Frequency Distribution For The Verbal Total Of Set 1 (The Easier Level) Of The New Test Of Memory, For The Control Group

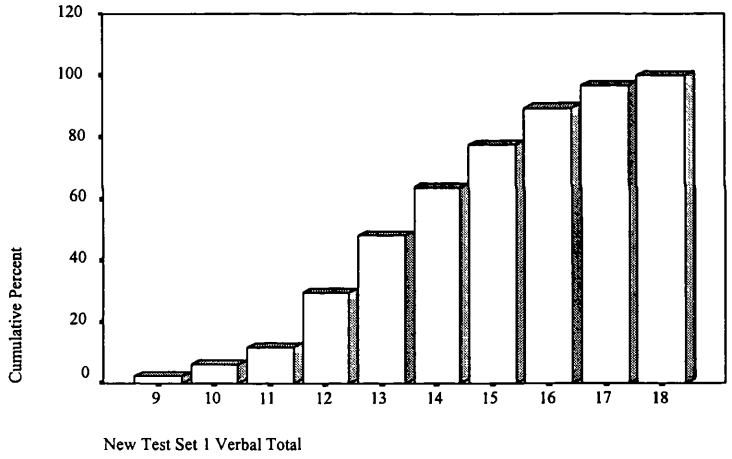


Figure 2.4.14: A Cumulative Frequency Distribution For The Verbal Total Of Set 2 (The More Difficult Level) Of The New Test Of Memory, For The Control Group

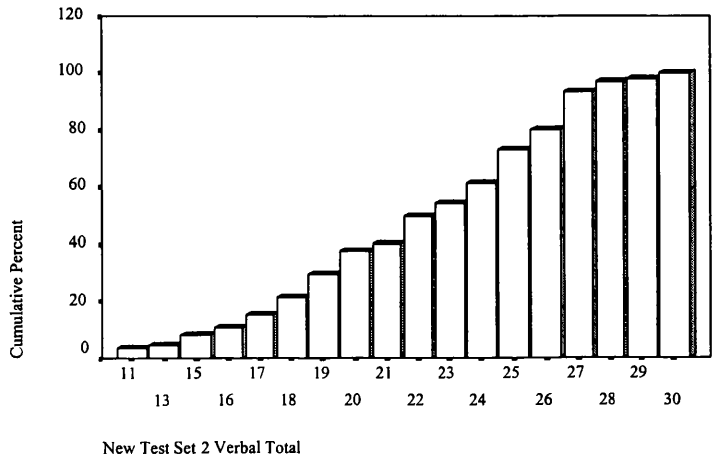


Figure 2.4.15: A Cumulative Frequency Distribution For The Spatial Total Of The New Test Of Memory, At The Task Familiarisation Stage, For The Control Group

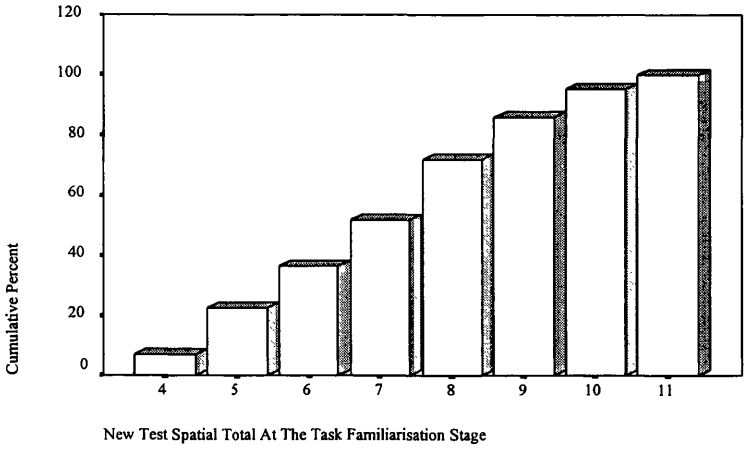


Figure 2.4.16: A Cumulative Frequency Distribution For The Spatial Total Of Set 1 (The Easier Level) Of The New Test Of Memory, For The Control Group

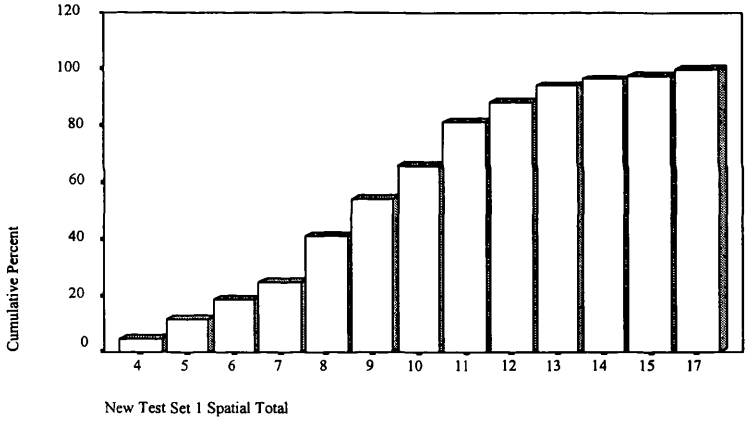


Figure 2.4.17: A Cumulative Frequency Distribution For The Spatial Total Of Set 2 (The More Difficult Level) Of The New Test Of Memory, For The Control Group

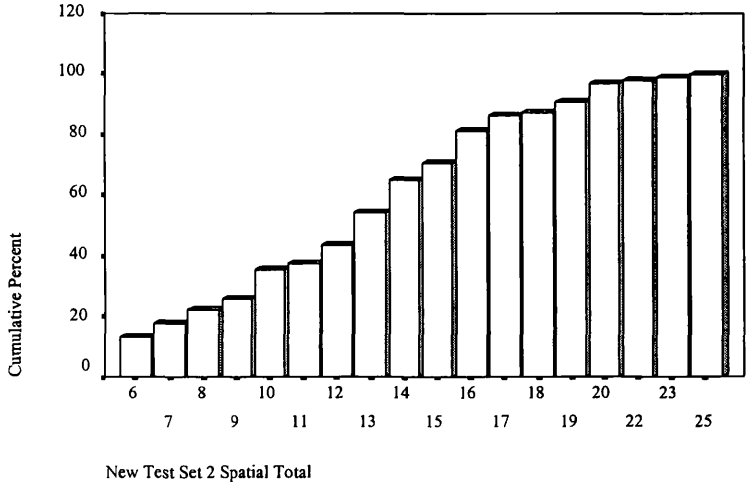
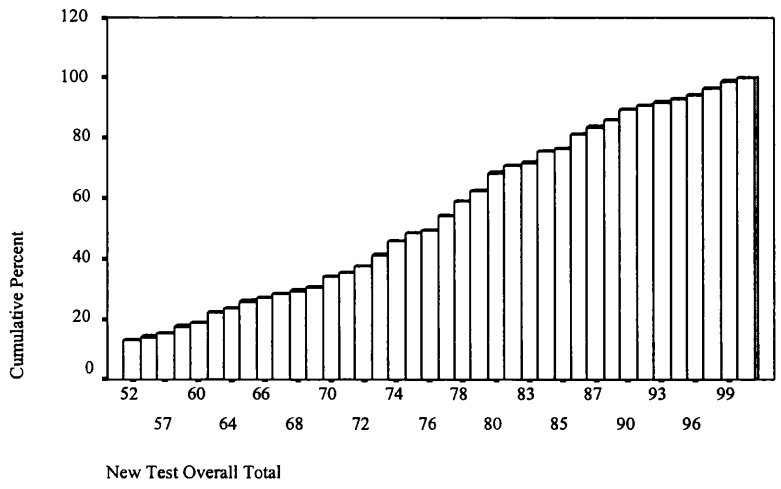


Figure 2.4.18: A Cumulative Frequency Distribution For The Overall Total Of The New Test Of Memory For The Control Group



As previously noted, two control subjects declined to complete the verbal sections of Set 2 (the more difficult level), while 10 subjects declined the spatial recall section, and eight individuals the spatial paired association and recognition sections. As there were no demographic or cognitive differences between the subjects who did and did not undertake Set 2, and it was desirable to have maximum numbers to allow Set 2 verbal and spatial totals to be compared with that of Set 1 (the easier level), multiple regression was used to predict these missing scores.

Set 2 verbal total was predicted from age group, NART-R IQ, Task Familiarisation verbal total, and Set 1 verbal total: $R^2 = 0.37$; significant F change = 0.001

Regression equation: - 0.383 -1.436 (age group) + 0.09856 (NART-R IQ) + 0.767 (Task Familiarisation verbal total) + 0.520 (Set 1 verbal total)

Set 3 spatial total was predicted from age group, sex, NART-R IQ, Task Familiarisation spatial total, and Set 1 spatial total: $R^2 = 0.43$; significant F change = 0.001

Regression equation: 7.524 - 1.051 (age group) - 1.958 (sex) + 0.0319 (NART-R IQ) + 0.286 (Task Familiarisation spatial total) + 0.617 (Set 1 spatial total)

As expected, when the predicted and actual values of subjects who completed Set 2 were compared the means were identical, hence, for individuals who failed to complete any section of Set 2, the predicted values were substituted. Having substituted the missing values in Set 2, the overall verbal and spatial totals for these individuals could also be calculated. The adjusted Set 2 verbal total mean (SD) was 22.32 (4.23), median (range) 23.00 (11-30), and overall verbal total mean (SD) 46.41 (6.37), median (range) 46.00 (30-56); for Set 2, the spatial total mean (SD) was 13.56 (4.04), median (range) 13.50 (6-25), and overall spatial total mean (SD) 30.19 (7.16), median (range) 30.50 (17-51).

2.4.8 Percentiles:

The purpose of the healthy control sample was to enable an accurate comparison of cognitive performance with the patient group, thus the age effects previously documented in the control data must be accommodated. Percentiles often prove useful in a clinical setting, therefore Table 2.4.16 shows the scores that lay on the 5^{th}, 25^{th}, and 50^{th} percentile of the cumulative frequency curves for the three age groups for verbal and spatial recall, paired association, and recognition, and for the verbal and spatial totals of the Task Familiarisation stage, and Sets 1 and 2, using the substituted scores

from the multiple regression where appropriate for verbal and spatial Set 2 totals, and therefore for the verbal and spatial overall totals.

Consideration of these cut offs allows the score distributions of each age band to be compared. The data set appears coherent, demonstrating consistent, regular age effects (with the exception of very few scores). Minor adjustments were made to smooth the data (original values shown in brackets). For controls aged 41 to 55 years, the 5th percentile of the verbal recognition total was adjusted to 12, the 5th percentile of the spatial paired association total was increased to 2, the 50th percentile of the spatial recognition total was altered to 12, and the 5th percentile of the spatial total Set 1 augmented to 5. For controls aged 56 to 70 years, the 5th percentile of the verbal paired association total was decreased to 7, and the 5th percentile of the verbal recognition total was adjusted to read 12.

Table 2.4.16: Age Cut Off Scores For The Three Age Bands Of The Control Group, For The New Test Of Memory

	controls age 18 to 40 years	controls age 41 to 55 years	controls age 56 to 70 years
Mean (SD) New Test **verbal RCLL total**	pc5: 13 pc25: 17 pc50: 19	pc5: 11 pc25: 13 pc50: 15	pc5: 9 pc25: 13 pc50: 15
Mean (SD) New Test **verbal PA total**	pc5: 7 pc25: 14 pc50: 15	pc5: 7 pc25: 12 pc50: 13	pc5: 7 (8) pc25: 11 pc50: 13
Mean (SD) New Test **verbal RECOG total**	pc5: 12 pc25: 16 pc50: 17	pc5: 12 (11) pc25: 15 pc50: 16	pc5: 12 (13) pc25: 15 pc50: 16

	controls age 18 to 40 years	controls age 41 to 55 years	controls age 56 to 70 years
Mean (SD) New Test **verbal total**	pc5: 38 pc25: 47 pc50: 50	pc5: 34 pc25: 42 pc50: 44	pc5: 32 pc25: 40 pc50: 44
Mean (SD) New Test **spatial RCLL total**	pc5: 7 pc25: 11 pc50: 14	pc5: 6 pc25: 9 pc50: 13	pc5: 5 pc25: 8 pc50: 12
Mean (SD) New Test **spatial PA total**	pc5: 3 pc25: 6 pc50: 7	pc5: 2 (1) pc25: 4 pc50: 7	pc5: 2 pc25: 3 pc50: 4
Mean (SD) New Test **spatial RECOG total**	pc5: 7 pc25: 11 pc50: 12	pc5: 6 pc25: 9 pc50: 12 (9)	pc5: 6 pc25: 8 pc50: 12
Mean (SD) New Test **spatial total**	pc5: 22 pc25: 28 pc50: 32	pc5: 18 pc25: 25 pc50: 30	pc5: 17 pc25: 21 pc50: 25
Mean (SD) New Test **verbal total TF**	pc5: 9 pc25: 10 pc50: 11	pc5: 7 pc25: 9 pc50:10	pc5: 7 pc25: 9 pc50: 10
Mean (SD) New Test **verbal total Set 1**	pc5: 12 pc25: 13 pc50: 14	pc5: 11 pc25: 12 pc50: 13	pc5: 9 pc25: 11 pc50: 13
Mean (SD) New Test **verbal total Set 2**	pc5: 16 pc25: 22 pc50: 25	pc5: 14 pc25: 18 pc50: 20	pc5: 11 pc25: 18 pc50: 20
Mean (SD) New Test **spatial total TF**	pc5: 4 pc25: 7 pc50: 8	pc5: 4 pc25: 6 pc50: 8	pc5: 4 pc25: 5 pc50: 6

	controls age 18 to 40 years	controls age 41 to 55 years	controls age 56 to 70 years
Mean (SD) New Test **spatial total Set 1**	pc5: 5 pc25: 8 pc50: 10	pc5: 5 (4) pc25: 8 pc50: 9	pc5: 5 pc25: 6 pc50: 8
Mean (SD) New Test **spatial total Set 2**	pc5: 7 pc25: 12 pc50: 15	pc5: 7 pc25: 10 pc50: 13	pc5: 6 pc25: 9 pc50: 11

TF = Task Familiarisation; RCLL = recall memory; PA = paired association; RECOG = recognition memory

2.4.9 Predicted Scores:

Multiple regression was used to obtain an equation for predicting the overall verbal and spatial total scores on the New Test Of Memory.

The verbal total was predicted from age group and NART-R IQ: $R^2 = 0.30$; significant F change = 0.001

Regression equation: 23.589 - 3.878 (age group) + 0.288 (NART-R IQ)

The spatial total was predicted from age group, sex, and NART-R IQ: $R^2 = 0.38$; significant F change = 0.001

Regression equation: 17.158 - 4.857 (age group) - 3.575 (sex) + 0.267 (NART-R IQ)

2.5 THE CONTROL SAMPLE: DISCUSSION

2.5.1 The New Test Of Memory:

The New Test Of Memory was developed to provide a reliable and valid assessment of verbal and spatial explicit recent memory. Administering the new measure to a healthy control sample allowed the assessment of the test's psychometric properties, and the appraisal of the assessment tool in the context of intact memory function.

2.5.1.1 Applicability:

The design of the new measure did not present any problems for the control sample, with all subjects (except one who has been previously discussed, Section 2.3.2) able to complete the Task Familiarisation phase and that of Set 1. Therefore, the format imposed by the requirement of applicability to patients with compromised sensori-motor skills did not render the test inappropriate for assessing memory in the normal population. It would appear that fine visual discrimination and competent manual dexterity are not necessary task demands to create a measure capable of spanning most of the normal ability spectrum.

2.5.1.2 Psychometric Properties:

The New Test Of Memory demonstrated internal reliability, with high values of Cronbach's Alpha (Section 2.4.5), indicating that the items comprising the verbal and the spatial sections of the measure assessed the same concept. In addition, the internal consistency of the test was illustrated by the moderate to strong correlations between the

verbal and spatial memory domains (Table 2.4.11), and the verbal and spatial composite scores for the Task Familiarisation stage, and Sets 1 and 2 (Table 2.4.12). These findings suggest that the New Test Of Memory, like conventional assessments, examines general memory ability, in addition to that of the particular memory domains.

None of the control subjects spontaneously reported that the New Test Of Memory did not assess memory, or was inappropriate, indicating that the measure possessed face validity. The construct validity of the New Test Of Memory was demonstrated by the expected moderate correlations of the composite verbal and spatial totals, and the overall total, with the assessments of general verbal and spatial skills (Table 2.4.13). These correlations suggest that the tasks share 'g'. The solutions of the factor analyses, both of which identified the strong verbal and spatial components of the new test, also indicate validity (Tables 2.4.14 & 2.4.15).

2.5.2 Discussion Of Findings:

2.5.2.1 Sample:

The control sample comprised 85 individuals with a broad range of ages and IQs, for both sexes. In the age group 18-40 years, a significant female preponderance was noted (Section 2.4.1). This may have exerted a mild influence on the mean scores recorded for the various sections of the new measure, however, as males are reported to demonstrate superior spatial visualisation and orientation skills, relative to females (McGee, 1979), any bias due to the predominance of females would only have had the potential to skew control results towards under achievement. In a comparison of the performance of patients relative to control, therefore, this would simply evince a more conservative pattern of deficiencies in the patient group.

2.5.2.2 Neuropsychological Features: Conventional Tasks

The mean NART-R IQ of the overall control sample was slightly above 100 (Table 2.4.3), which is a consistent finding in control groups at this and other metropolitan centres. It is thought to reflect the higher prevalence of professionals relative to unskilled workers, employed by corporation headquarters, which are often located in large city centres. In the older age groups of the control sample, especially at the lower end of the ability spectrum, recruitment was problematic. Healthy volunteers aged 56-70 years were the least accessible, as several of the organisations from which volunteers were recruited did not employ many individuals over 56 years, and subjects who volunteered through their Women's Institute or Social Club tended to be highly motivated and articulate. Healthy individuals aged 56-70 years were often difficult to approach and reluctant to participate in a study which involved memory tasks. This may have been due to fears of exposing deficits.

The mean NART-R IQ of the 56-70 years age group of the control sample was significantly higher than that of the age group 18-40 years (Table 2.4.4). However, as the effects of intelligence on memory may be less pronounced than those of ageing (Walton & Black, 1957; Newcombe & Steinberg, 1964; Bornstein & Chelune, 1988; Ruff et al., 1988), this finding is unlikely to bias the results significantly. In addition, mean scaled score on the vocabulary subtest of the WAIS-R (Wechsler, 1981), and the mean equivalent IQ on the spatial analogy section of the VESPAR (Langdon & Warrington, 1995), did not differ significantly between the three age groups (Table 2.4.4).

The 95% confidence limits around the mean NART-R IQ, mean scaled score from using the vocabulary subtest of the WAIS-R, and mean equivalent IQ using the spatial analogy section of the VESPAR, for the control sample as a whole, and when

divided into the three age groups, were small (Tables 2.4.3 & 2.4.4), suggesting that accuracy had been achieved. The 95% confidence interval has probability of 0.95 of containing the population value (Armitage & Berry, 1994), and if the limits are close to the mean value reported, they indicate that there may be generalisability from the results.

2.5.2.3 Neuropsychological Features: The New Test Of Memory

The control sample demonstrated a range of scores on the verbal and spatial recall, paired association, and recognition sections of the New Test Of Memory, at the Task Familiarisation stage, and at the two levels of difficulty (Tables 2.4.5, to 2.4.7). The 95% confidence limits around the composite scores were small (Tables 2.4.6 & 2.4.7), again illustrating that the control sample is probably providing a true representation of the general population, and hence permitting generalisability from the results.

The cumulative frequency graphs illustrated the range of scores attained for the various memory domains, and the verbal and spatial totals at the Task Familiarisation stage, and the two difficulty levels (Figures 2.4.4 to 2.4.18). Verbal and spatial recall, paired association, and recognition sections, appeared to cover a wide range of memory functions, and grade ability. The score distributions approximated the normal curve for verbal recall, and spatial recall, paired association, and recognition, but were skewed to the right, towards ceiling level for the verbal paired association and verbal recognition sections. This finding suggests that high level ability in these verbal memory domains may not be differentiated by the new test, that is, it may lack sensitivity at this advanced level of capability. However, it is unlikely that this will be a major limiting factor,

because discriminating among excellent memory performances has little clinical relevance. The two difficulty levels of the new measure also appeared sensitive to the range of memory capabilities exhibited by the controls, suggesting that these levels spanned the normal ability spectrum.

The well documented effects of age on memory were consistently demonstrated by the new test (Tables 2.4.6, to 2.4.8). These are of special interest because conventional memory assessments often place considerable demands on efficient sensori-motor and linguistic skills, which may insidiously decline with age, and therefore conventional test formats may penalise older subjects. However, the age effects exhibited on all sections of the New Test Of Memory imply these previous findings are genuine memory effects. Despite these results using the New Test Of Memory, it must be noted that these data have been collected on only one occasion, that is, the findings are based on a cross-sectional study, therefore, it is not possible to eliminate cohort effects as an explanation for the gradient of memory performance across the age groups. A longitudinal follow-up, documenting the serial performance of the healthy controls on the new measure, would confirm the negative effects of age on memory.

Performance on the verbal and spatial Task Familiarisation stage of the New Test Of Memory did not correlate significantly with NART-R IQ (Tables 2.4.9 & 2.4.10), which suggests that level of intelligence, within the normal range, does not affect ability to learn the relatively simple tasks involved, and supports the idea that the training phase utilises procedural memory. The correlations of performance on the Task Familiarisation phase with that of Sets 1 and 2 (Table 2.4.12) illustrated that there is a significant relationship between training and declarative memory performance. This provides support for the inclusion of the scores on the Task Familiarisation phase in the

composite totals on the New Test Of Memory, and demonstrates that learning the actual task is an integral part of overall memory performance.

A relatively small number of controls declined to complete Set 2 (the more difficult level), and, as they did not differ demographically, or cognitively (including performance on the Task Familiarisation stage, and Set 1 of the New Test Of Memory), from those who went on to complete Set 2, multiple regression was used to predict their scores. One of the problems of using a multiple regression equation and substituting the values for missing data is that the standard deviation of the predicted values will be smaller than the standard deviation of the data collected. However, the number of substitutions was limited, and the procedure was adopted in the later stages of the analyses, therefore the psychometric properties of the new measure were evaluated before the insertion of the predicted scores, and were thus free of any additional error variance.

2.6 THE CONTROL SAMPLE: CONCLUSIONS

Thus if can be seen that the control sample provides coherent normative data of performance on the New Test Of Memory against which the memory functions of patients with MS can be assessed. The format of the test is appropriate for the assessment of memory in subjects with intact memory function, and the analyses of its psychometric properties have demonstrated that it is a reliable and homogeneous measure, which also demonstrates validity. The control sample spanned a wide range of ages and levels of intelligence for both sexes, and their performance on the New Test Of Memory demonstrated that the measure covered the ability spectrum for the various memory domains, and both difficulty levels. The control sample can therefore be used to allow detailed assessment of the memory abilities of patients with MS.

2.7 THE PATIENT SAMPLE: METHOD

All patients (N=100) completed the same brief neuropsychological battery as the control subjects. This lasted approximately one hour, and details can be found in Section 2.7.1. The neuropsychological measures used were selected because they were considered to be robust to sensori-motor dysfunction. In addition, the patients who were recruited from the Neuro-Rehabilitation Unit (N=50), completed a number of supplementary cognitive tasks (Section 2.7.1), taking a further two or three hours. The two patient groups are henceforth referred to as completing "the short battery" and "the long battery"; the latter term applying to the more extensive range of tests which 50 patients undertook.

2.7.1 Test Battery And Administration Procedures:

The entire patient group completed the same tests as the controls, details of which can be found in Section 2.3.1:

1) NART-R (Nelson & Willison, 1992). Section 2.3.1.

2) Vocabulary subtest of the WAIS-R (Wechsler, 1981). Section 2.3.1.

3) Spatial analogy section of the VESPAR (Langdon & Warrington, 1995). Section 2.3.1.

4) The New Test Of Memory. Section 2.2.

5) HADS (Zigmond & Snaith, 1983). Section 2.3.1.

6) NHPT (Mathiowetz et al., 1985). Section 2.3.1.

Details of patients' disease type, duration, and medication were retrieved from the medical notes, and all patients were examined by a neurologist, who scored each individual on the Expanded Disability Status Scale (EDSS, Kurtzke, 1983). The EDSS

is a 10 point ordinal scale, which assesses the level of impairment and disability of a given patient. It is widely used by neurologists.

Half of the patients (N=50) were recruited from the inpatient Neuro-Rehabilitation Unit (NRU) of a teaching hospital, and completed a number of additional neuropsychological tests, namely:

8) Digit span, arithmetic and similarities subtests of the WAIS-R (Wechsler, 1981). The digit span task has already been detailed in the introduction (Section 1.9.1.1). The arithmetic section requires the subject to solve 14 mathematical problems, which are read aloud; pencil and paper are not permitted. The similarities subtest requires the subject to explain how a series of 14 pairs of items are alike. These three subtests, together with the vocabulary subtest, allowed the pro-rated calculation of current verbal IQ, an international benchmark for the calibration of intelligence.

9) Spatial categorisation and series completion sections of the VESPAR (Langdon & Warrington, 1995). These two sections examine the relevant inductive reasoning skills using two sets of 25, four alternative multiple choice problems, and provide a comprehensive measure of general spatial reasoning ability.

10) Trials 1 to 5 of the California Verbal Learning Test (CVLT, Delis et al., 1987), details of which can be found in the introduction (Section 1.9.2.3).

11) Recognition Memory Test for Words (RMTW, Warrington, 1984), which is detailed in the introduction (Section 1.9.1.3).

12) Visual memory span, figural memory, logical memory I, visual reproduction I, verbal paired associates I, and visual paired associates I subtests of the Wechsler Memory Scale - Revised (WMS-R, Wechsler, 1987), all of which are detailed in the introduction (Section 1.9.1.2).

These same patients were comprehensively assessed by a multidisciplinary team, and therefore the additional information of visual acuity, Functional Systems scores, and their ability on two extra impairment and disability scales was also available. These supplementary measures were:

13) Functional Independence Measure (FIM, Keith et al., 1987). The FIM provides an extensive measure of disability relating to everyday activities, which encompasses communication and cognitive function as well as self care activities and mobility. It is an interval scale with a range of scores from 13 to 126. The scale comprises 18 items; 13 motor items, categorised under the headings self care, locomotion, mobility, and sphincter control, and five cognitive items which are comprehension, expression, social interaction, problem solving, and memory.

14) A modified version of the Barthel Index (Mahoney & Barthel, 1965; Collin et al., 1988). The Barthel index is an ordinal scale with a range of scores from 0 to 20, which is used in the assessment of level of independence in basic functions of daily living. It covers selective tasks, namely, bladder and bowel management, toilet use, bathing, dressing, grooming, feeding, transfers, stairs, and mobility.

As noted in Section 2.3.1 for the control subjects, standardised administration procedures were again adopted for all neuropsychological assessments, and the order in which the tests were given to the patients was randomised, to minimise the effects of fatigue, practice, or other variables from introducing a systematic bias into the results. Likewise, with the New Test Of Memory, whether the subject first received the verbal or spatial sections of each set was also randomised. All patients were assessed individually in a quiet room, with minimal distraction. For the purposes of their rehabilitation programme, 32 subjects were initially given clinical cognitive assessments, hence the VIQ and RMTW had already been administered. This was not

thought to prejudice the results to any significant degree, because standard administration procedures are routinely adopted by all members of the department. The battery of neuropsychological tests undertaken by the inpatients recruited from the Neuro-Rehabilitation Unit (NRU), which included a number of supplementary measures, required at least three sessions (45 minutes to one hour). These were completed within 72 hours for the majority of patients, and for all subjects within a maximum time span of seven days. The assessment period for patients who completed the shorter battery of cognitive tasks was approximately one hour.

2.7.2 Subjects:

The patient sample comprised 100 individuals with clinically or laboratory supported definite MS (Poser et al., 1983). 45 of these patients were recruited from the outpatient clinics of Professors A.J. Thompson, D.H. Miller, and W.I. McDonald, consultant neurologists at the National Hospital for Neurology and Neurosurgery, and five were inpatients of the same consultants. The remaining 50 subjects were inpatients recruited from the NRU of the National Hospital for Neurology and Neurosurgery. The study was approved by the joint ethics committee of the Institute of Neurology and National Hospital for Neurology and Neurosurgery, and following detailed discussion with each patient concerning the nature and purpose of the project, together with a written information sheet (a copy of which can be found in Appendix I), all subjects gave informed consent. Patients were excluded from the study if: English was not their first language, they had additional neurological or psychiatric disease which it was considered may impact on their performance, or they had completed other neuropsychological assessments and therefore were familiar with the stimuli and tasks.

The 50 subjects from the NRU were recruited from all the MS patients referred to the unit between November, 1997 and November, 1998. Three patients were not recruited because English was not their first language, two subjects were excluded from the study because their visual acuity was so poor that they were registered as partially sighted, two patients exhibited significant behavioural problems that made them inappropriate to assess, and two subjects were not approached because they were not test naïve having been frequently cognitively assessed over the past 24 months. A further five patients declined any cognitive assessment, for either clinical or research purposes.

Table 2.7.1 shows the number of patients who completed each section of the test battery.

Table 2.7.1: The Number Of Patients Who Completed Each Section Of The Neuropsychological Test Battery

Neuropsychological Test	No. short batt.	No. long batt.
NART-R	50	50
Vocabulary (WAIS-R)	49	50
Spatial Analogy (VESPAR)	46	49
New Test Verbal TF RCLL	50	50
PA	50	50
RECOG	50	50
New Test Verbal Set 1 RCLL	50	50
PA	50	50
RECOG	50	50
New Test Verbal Set 2 RCLL	42	45
PA	42	45
RECOG	42	45

Neuropsychological Test	No. short batt.	No. long batt.
New Test Spatial TF RCLL	49	50
PA	50	50
RECOG	50	50
New Test Spatial Set 1 RCLL	49	50
PA	50	50
RECOG	50	50
New Test Spatial Set 2 RCLL	40	38
PA	41	39
RECOG	41	39
Spatial Categorisation (VESPAR)	-	49
Spatial Series (VESPAR)	-	49
VIQ (WAIS-R)	-	50
RMTW	-	50
CVLT	-	49
Visual Memory Span (WMS-R)	-	49
Figural Memory (WMS-R)	-	49
Visual Reproduction I (WMS-R)	-	45
Verbal Paired Associates I (WMS-R)	-	50
Visual Paired Associates I (WMS-R)	-	49

TF = Task Familiarisation; RCLL = recall memory; PA = paired association; RECOG = recognition memory

Of the NRU patients, one subject was unable to complete the visual memory span, visual reproduction I, figural memory, and visual paired associates I subtests of the WMS-R, and all sections of the VESPAR, due to poor visual acuity (right eye 6/18; left eye finger counting). A further four patients were unable to complete the visual reproduction I subtest of the WMS-R because their manual dexterity was so poor that it

rendered them incapable of holding a pen. For the CVLT, data was missing on one patient, as they were unexpectedly discharged before this could be administered. On the New Test Of Memory: five patients declined to complete any of Set 2 (the more difficult level), an equal number declined all spatial sections, a further two patients declined the Set 2 spatial recall subtest, and one subject Set 2 spatial paired association and recognition sections. With respect to missing data for the short battery patients: one subject was very short of time and was unable to stay to complete the vocabulary subtest of the WMS-R and the spatial analogy section of the VESPAR; similarly, a further three subjects did not complete the spatial analogy section of the VESPAR due to time pressures. On the New Test Of Memory: one subject did not complete any of the spatial recall sections, not even the Task Familiarisation stage, due to shortage of time, and the author considered these sections took comparatively longer, relative to the number of other tasks which could be completed in the same period; eight subjects did not complete any of Set 2 (the more difficult level), an additional one individual declined the Set 2 spatial subtests. In all these cases subjects declined because time was limited or they expressed fatigue. Inspection of the table showed that the amount of missing data was acceptable for a research project based on a clinical population of chronically ill patients, and a Mann-Whitney test with a Bonferroni Correction for multiple tests (Bland & Altman, 1995) failed to find a significant difference between the demographic and clinical characteristics, or the Task Familiarisation stage and Set 1 (the easier level), verbal and spatial recall, paired association, and recognition scores of those who did and did not go on to complete Set 2. It was unlikely, therefore, that the missing data would have biased the results in a significant manner.

2.8 THE PATIENT SAMPLE: RESULTS

2.8.1 Demographic And Clinical Characteristics:

Table 2.8.1 details the demographic and clinical characteristics of the patient sample as a whole. The preponderance of female subjects reflects the well documented 1:2 male:female sex ratio found in relapsing-remitting and secondary progressive MS. When comparing the demographic details of the patient group as a whole with those of the controls, also presented in Table 2.8.1 for the purposes of comparison, it can be seen that the patients were significantly more likely to be coded in the occupational bracket of "retired/housewife/unemployed" (Mann-Whitney Test with Bonferroni Correction, Bland & Altman, 1995). In addition, the patients took significantly longer to complete the NHPT with either hand, than the controls, and were significantly more depressed according to the HADS (Mann-Whitney Test with Bonferroni Correction, Bland & Altman, 1995). These findings are unremarkable, as the patients recruited were suffering from a chronic disease of the central nervous system, which can result in marked disability, hence the fewer subjects in employment, their slowness on the NHPT, and the increased incidence of depression.

The patient group demonstrated the same sex distribution as the control group. A chi-square test showed that there was a significantly greater number of women in the patient sample ($\chi^2 = 9.000$; df = 1; p = 0.003), however, this bias did not vary significantly when the sample was divided into the three age groups ($\chi^2 = 0.212$; df = 2; p = 0.899). The higher frequency of female patients only reached significance in the age group 18 to 40 years ($\chi^2 = 4.900$; df = 1; p = 0.027).

Table 2.8.2 shows the separate demographic and clinical details for the two patient groups, who completed the long and short neuropsychological test batteries.

Using a Mann-Whitney test with Bonferroni Correction for multiple tests (Bland & Altman, 1995), the only significant differences between these two groups were: whether patients had children (not considered to be relevant to cognitive performance), educational level (a crude measure, Table 2.8.4 shows NART-R IQ which was not significantly different, between the two group), type of MS, EDSS, and time to complete the NHPT. Long battery patients were recruited from the NRU where the purpose of their hospitalisation was inpatient rehabilitation, thus the bias towards secondary progressive MS, and hence greater disability is unsurprising.

Table 2.8.1: Demographic And Clinical Characteristics For The Patient Group (N=100)

	Patients (N=100)	Controls (N=85)
Sex (Male:Female)	35:65	29:56
Age in years: mean (SD)	45.01 (11.00)	43.42 (12.39)
median (range)	44.50 (27-70)	44.00 (21-67)
Ethnic Group: Caucasian	96	81
Afro/Caribbean	1	1
Asian/Asian Pacific	2	3
Other	1	0
Marital Status:		
Single	28	28
Married	59	49
Divorced/Separated	10	6
Widowed	3	2
No. of subjects with children	61	52
No. of subjects without children	39	33

	Patients (N=100)	Controls (N=85)
Educational Level:		
no qualifications	23	17
'O' levels/CSEs/GCSEs	24	32
'A' levels	19	12
Degree	34	24
Current Occupation/Social Class:		
professional	6	7
managerial & technical	25	24
skilled occupations	13	38
partly skilled	0	0
retired/housewife/unemployed	56	16
Dominant Hand: right	84	76
left	16	9
NHPT in seconds:		
dominant hand mean (SD)	32.38 (10.80)	18.39 (2.52)
median (range)	29.90 (14.84-61.10)	18.04 (14.37-25.44)
No. of subjects unable to complete task	14	0
non dominant hand mean (SD)	35.59 (16.90)	19.45 (3.04)
median (range)	30.05 (16.75-108.27)	19.09 (15.03-30.31)
No. of subjects unable to complete task	18	0
HADS: total score mean (SD)		
anxiety score mean (SD)	12.73 (6.45)[1]	9.92 (4.55)[4]
depression score mean (SD)	7.23 (4.01)[1]	6.58 (2.91)[4]
Disease Type: relapsing-remitting	25	-
primary progressive	10	-
secondary progressive	61	-
transitional progressive	0	-
benign	4	-
[2]**Disease Duration in years:**		
mean (SD)	10.06 (7.02)	-
median (range)	8.00 (0.25-31.00)	-

	Patients (N=100)	Controls (N=85)
[2] **Age At Onset:** mean (SD)	34.93 (10.50)	-
median (range)	32.00 (16-67)	-
[3]**EDSS:** mean (SD)	6.17 (1.80)	-
mode	6.5	-
median (range)	6.5 (1.5-9.0)	-
No. of subjects on medication	70	-
No. of subjects not on medication	30	-

Disease Duration and Age At Onset taken from diagnosis

[1] data based on 95 patients, i.e. 5 patients missing; [2] data based on 99 patients, i.e. 1 patient missing; [3] data based on 92 patients, i.e. 8 patients missing; [4] data based on 83 controls, i.e. 2 individuals missing

Table 2.8.2: Demographic And Clinical Details Of The Patient Group (Divided Into Short And Long Battery Subjects)

	Short Battery Patients (N=50)	Long Battery Patients (N=50)
Sex (Male:Female)	18:32	17:33
Age in years: mean (SD)	42.46 (11.12)	47.56 (10.36)
median (range)	41.50 (27-70)	49.00 (30-68)
Ethnic Group: Caucasian	47	49
Afro/Caribbean	0	1
Asian/Asian Pacific	2	0
Other	1	0
Marital Status: Single	20	8
Married	24	35
Divorced/Separated	4	6
Widowed	2	1
No. of patients with children	22	39
No. of patients without children	28	11

	Short Battery Patients (N=50)	Long Battery Patients (N=50)
Educational Level:		
no qualifications	6	17
'O' levels/CSEs/GCSEs	11	13
'A' levels	9	10
Degree	24	10
Current Occupation/Social Class:		
professional	6	0
managerial & technical	15	10
skilled occupations	8	5
partly skilled	0	0
retired/housewife/unemployed	21	35
Dominant Hand: right	39	45
left	11	5
NHPT in seconds:		
dominant hand mean (SD)	28.79 (10.56)	36.32 (9.75)
median (range)	26.75 (14.84-60.78)	33.20 (20.11-61.10)
No. of patients unable to complete task	5	9
non dominant hand mean (SD)	32.42 (14.61)	39.27 (18.75)
median (range)	28.00 (16.75-103.65)	33.85 (21.11-108.27)
No. of patients unable to complete task	6	12
HADS: total score mean (SD)	12.34 (7.03)[1]	13.10 (5.88)[4]
anxiety score mean (SD)	7.11 (4.42)[1]	7.35 (3.61)[4]
depression score mean (SD)	5.23 (3.62)[1]	5.75 (3.26)[4]
Disease Type: relapsing-remitting	21	4
primary progressive	7	3
secondary progressive	18	43
transitional progressive	0	0
benign	4	0

	Short Battery Patients (N=50)	Long Battery Patients (N=50)
Disease Duration in years:		
mean (SD)	8.71 (6.70)[2]	11.38 (7.15)
median (range)	6.0 (1.00-31.00)[2]	10.50 (0.25-27.00)
Age At Onset: mean (SD)	33.65 (10.01)[2]	36.19 (10.88)
median (range)	30.00 (16-58)[2]	34.5 (16-67)
EDSS: mean (SD)	5.33 (2.20)[3]	6.87 (0.95)
mode	6.0[3]	6.5
median (range)	6.0 (1.5-8.5)[3]	6.5 (3.5-9.0)
No. of patients on medication	30	40
No. of patients not on medication	20	10

Disease Duration and Age At Onset taken from diagnosis
[1] data based on 47 patients, i.e. 3 patients missing; [2] data based on 49 patients, i.e. 1 patient missing; [3] data based on 42 patients, i.e. 8 patients missing; [4] data based on 48 patients, i.e. 2 patients missing

In addition to the visual section of the Functional Systems recorded for all NRU patients, details of these patients' visual acuity were taken from the neurological examination, where different measures were employed. The values range from 6/6 uncorrected to finger counting and from N10 corrected to N48 uncorrected.

2.8.2 Performance On Neuropsychological Tests:

Table 2.8.3 shows the performance of the patient group as a whole on established neuropsychological tests. The control scores are given for comparative purposes, and it can be seen that the patient group as a whole did not differ significantly from the control sample with respect to mean premorbid IQ, or mean score on the measures of general verbal and spatial skills (Mann-Whitney with a Bonferroni Correction for multiple tests, Bland & Altman, 1995). Table 2.8.4 gives the scores on these neuropsychological tasks, for the short and long battery groups separately. There

were no significant differences between the performance of the two patient samples on any of these measures (Mann-Whitney test with Bonferroni Correction for multiple tests, Bland & Altman, 1995). Tables 2.8.3 and 2.8.4 also detail the 95% confidence limits around the mean values attained by the patients, on each of the neuropsychological tasks administered. It can be seen that in the majority of cases these limits are close to the mean, suggesting accuracy, and indicating that the patient sample is a relatively reliable estimate of the performance of the MS population. Raw scores can be found in Appendix J.

Table 2.8.3: Mean, Standard Deviation, And 95 % Confidence Intervals For The Cognitive Scores Of The Patient Group

	Patients (N=100)	Controls (N=85)
NART-R:		
full scale IQ mean (SD)	105.62 (13.60)	103.22 (10.17)
median (range)	107.50 (70-129)	103.00 (80-120)
95% confidence limits	102.91-108.33	101.02-105.42
[1]**WAIS-R: vocabulary subtest**		
scaled score mean (SD)	9.66 (2.35)	9.26 (2.13)
median (range)	10.00 (2-14)	9.00 (6-15)
95% confidence limits	9.19-10.13	8.80-9.72
[2]**VESPAR:**		
spatial analogy section		
equivalent IQ mean (SD)	101.86 (9.86)	105.59 (5.88)
median (range)	104.00 (78-121)	106.00 (90-117)
95% confidence limits	99.85-103.87	104.32-106.86

[1] data based on 99 patients, i.e. 1 patient missing
[2] data based on 95 patients, i.e. 5 patients missing

Table 2.8.4: Mean, Standard Deviation, And 95% Confidence Intervals For The Cognitive Scores Of The Patient Group (Divided Into Short And Long Battery Subjects)

	Short Batt. Patients (N=50)	Long Batt. Patients (N=50)
NART-R:		
full scale IQ mean (SD)	107.18 (12.36)	104.06 (14.69)
median (range)	107.50 (79-127)	107.50 (70-129)
95% confidence limits	103.67-110.69	99.88-108.24
[1]**WAIS-R:**		
vocabulary subtest		
scaled score mean (SD)	9.90 (2.28)[1]	9.42 (2.43)
median (range)	10.00 (5-14)[1]	10.00 (2-14)
95% confidence limits	9.25-10.55	8.73-10.11
VESPAR:		
spatial analogy section		
equivalent IQ mean (SD)	103.48 (10.13)[2]	100.35 (9.46)[3]
median (range)	106.50 (78.-121.)[2]	103.00 (78-119)[3]
95% confidence limits	100.47-106.49	97.63-103.07

[1] data based on 49 patients, i.e. 1 patient missing
[2] data based on 46 patients, i.e. 4 patients missing
[3] data based on 49 patients, i.e. 1 patient missing

The NRU patients completed a more comprehensive battery of neuropsychological tasks, and their performance is detailed in Table 2.8.5. For the WAIS-R and RMTW scaled scores are given as these are an international reference set, and allow the subtests to be easily compared with each other. Raw scores can be found in Appendix K.

Table 2.8.5: Mean, Standard Deviation, And 95% Confidence Intervals For The Cognitive Scores Of The Patients Who Completed A Larger Battery Of Neuropsychological Tests (N=50)

WAIS-R:	
digit span subtest scaled score mean (SD)	8.74 (2.76)
median (range)	8.00 (4-15)
arithmetic subtest scaled score mean (SD)	8.20 (3.30)
median (range)	7.00 (2-15)
similarities subtest scaled score mean (SD)	8.82 (2.79)
median (range)	9.00 (3-15)
prorated sum of scaled scores mean (SD)	53.00 (14.03)
median (range)	51.75 (29-84)
verbal IQ mean (SD)	95.58 (13.87)
median (range)	94.50 (71-127)
95% confidence limits	91.64-99.52
[1]**VESPAR: spatial odd one section**	
equivalent IQ mean (SD)	103.92 (4.69)
median (range)	104.00 (90-114)
95% confidence limits	102.57-105.27
spatial series section	
equivalent IQ mean (SD)	102.76 (9.22)
median (range)	106.00 (72-118)
95% confidence limits	100.11-105.41
total raw score mean (SD)	51.04 (10.98)
median (range)	53.00 (27-68)

[2]WMS-R:	
visual span subtest raw score mean (SD)	13.67 (3.00)
median (range)	14.00 (6-21)
visual span forward raw score mean (SD)	7.24 (1.71)
median (range)	7.00 (2-11)
visual span backward raw score mean (SD)	6.43 (1.72)
median (range)	6.00 (2-10)
digit span forward raw score mean (SD)	7.52 (2.26)
median (range)	7.00 (4-13)
digit span backward raw score mean (SD)	6.22 (2.45)
median (range)	6.00(2-12)
figural memory subtest raw score mean (SD)	6.43 (1.72)
median (range)	6.00 (2-10)
verbal paired associates raw score mean (SD)	14.34 (4.36)
median (range)	14.00 (5-22)
visual paired associates raw score mean (SD)	10.63 (4.23)
median (range)	11.00 (0-17)
visual reproduction raw score mean (SD)	27.89 (8.23)
median (range)	28.00 (2-40)
RMTW:	
scaled score mean (SD)	9.08 (3.72)
median (range)	10.00 (3-15)
[1]CVLT:	
raw score trial 1 mean (SD)	5.51 (2.51)
median (range)	5.00 (1-14)
raw score trial 5 mean (SD)	10.43 (3.26)
median (range)	11.00 (4-16)
total score (trial 1-trial 5) mean (SD)	41.49 (13.08)
median (range)	4.00 (18-75)

[1] data based on 49 patients, i.e. 1 patient missing; [2] data based on 49 patients, i.e. 1 patient missing, apart from the verbal paired associates subtest, where N=50 and visual reproduction subtest based on 45 patients, i.e. 5 patients missing

The battery of tasks the NRU patients completed included a number of memory assessments; therefore, for each measure, using the published control data provided, the number of patients who scored at or below two SDs of the mean of the appropriate age group of controls was calculated. These data are presented in Table 2.8.6. It can be seen that on these conventional memory tests few patients were impaired on the span memory assessments. An equally small number of subjects performed at or below two SDs of the control mean on the verbal and nonverbal recognition memory tasks. Approximately half of the patient group were impaired on the verbal recall and verbal paired associates measures, with a smaller number of subjects impaired on the visual paired associates test. It should be noted, however, that these assessments have all been criticised as inappropriate for patients with MS, because the patients are automatically penalised by their restricted sensori-motor skills; for example, five subjects were unable even to attempt the visual reproduction subtest of the WMS-R due to poor manual dexterity and visual acuity. In addition, one of these patients was also unable to complete the visual paired associates, figural memory, and visual memory span subtests.

Table 2.8.6: Number Of Patients Scoring At Or Below Two SDs Of The Published Control Mean On The Conventional Tests Of Memory, And At Or Below The 5th, 25th, And 50th Percentile, Where Available

	Number (%) of patients at or below 2 SDs	Percentage of patients at or below published control sample percentiles: 5	25	50
[1]**WMS-R:**				
visual memory span	3 (6.1)	-	-	-
visual memory span forward	8 (16.3)	16.3	30.6	63.3
visual memory span backward	3 (6.1)	6.1	32.7	61.2
digit span	5 (10.2)	-	-	-
digit span forward	4 (8.2)	16.3	51.0	63.3
digit span backward	2 (4.1)	6.1	32.7	53.1
figural memory	3 (6.1)	-	-	-
verbal paired associates	22 (44.0)	-	-	-
visual paired associates	7 (14.3)	-	-	-
visual reproduction	7 (15.6)	13.3	44.4	66.7
RMTW:	8 (16.0)	16.0	48.0	56.0
[2]**CVLT:** score on trial 1	26 (53.1)	-	-	-
score on trial 5	25 (51.0)	-	-	-

[1] data based on 49 patients, i.e. 1 patient missing, apart from the verbal paired associates subtest, where N=50, and visual reproduction subtest based on 45 patients, i.e. 5 patients missing; [2] data based on 49 patients, i.e. 1 patient missing

2.8.3 New Test Of Memory:

Table 2.8.7 details the performance of the patient sample on the New Test Of Memory, while Tables 2.8.8 and 2.8.9 give their composite scores on the verbal and spatial recall, paired association, and recognition sections, and the verbal and spatial totals for the Task Familiarisation stage and the two difficulty levels respectively; control values are provided for the purposes of comparison. The 95% confidence limits

around the mean values attained by the patients, on each composite section of the New Test Of Memory are also given in Tables 2.8.8 and 2.8.9. It can be seen that in the majority of cases these limits are close to the mean, suggesting accuracy, and indicating that the patient sample is a relatively reliable estimate of the performance of the target MS population.

Comparing the mean scores of the patients with those of controls using a Mann-Whitney test with a Bonferroni Correction for multiple tests (Bland & Altman, 1995), it was found that the patients performed significantly below the controls on verbal recall, paired association, and recognition total, and spatial recall. The means were also significantly different for the composite verbal and spatial total scores, and the overall total. When performance at the Task Familiarisation stage, and Sets 1 and 2 were examined, the patients performed significantly below the controls at the initial training phase and at both verbal and spatial levels.

Table 2.8.7: Raw Scores On The New Test Of Memory For The Patient Group

Verbal Memory TF:	
RCLL mean (SD)	4.45 (1.20)
median (range)	5.00 (0-6)
PA mean (SD)	2.51 (0.70)
median (range)	3.00 (0-3)
RECOG mean (SD)	2.59 (0.64)
median (range)	3.00 (0-3)
Verbal Memory Set 1:	
RCLL mean (SD)	4.58 (1.89)
median (range)	4.00 (1-9)
PA mean (SD)	3.71 (1.15)
median (range)	4.00 (0-5)
RECOG mean (SD)	4.33 (0.77)
median (range)	4.00 (0-5)

[1]**Verbal Memory Set 2:**	
RCLL mean (SD)	5.90 (2.30)
median (range)	6.00 (1-11)
PA mean (SD)	5.98 (2.05)
median (range)	8.00 (1-9)
RECOG mean (SD)	7.36 (1.61)
median (range)	8.00 (2-9)
Spatial Memory TF:	
RCLL mean (SD)	2.99 (1.45)[2]
median (range)	3.00 (0-6)[2]
PA mean (SD)	1.29 (0.87)
median (range)	1.00 (0-3)
RECOG mean (SD)	2.15 (0.89)
median (range)	2.00 (0-3)
Spatial Memory Set 1:	
RCLL mean (SD)	2.99 (1.70)[2]
median (range)	3.00 (0-8)[2]
PA mean (SD)	1.90 (1.05)
median (range)	2.00 (0-4)
RECOG mean (SD)	2.86 (1.25)
median (range)	3.00 (0-5)
Spatial Memory Set 2:	
RCLL mean (SD)	4.00 (2.36)[3]
median (range)	4.00 (0-10)[3]
PA mean (SD)	2.16 (1.11)[4]
median (range)	2.00 (0-4)[4]
RECOG mean (SD)	4.83 (1.81)[4]
median (range)	5.00 (1-9)[4]

TF = Task Familiarisation; RCLL = recall memory; PA = paired association; RECOG = recognition memory

[1] based on 87 patients, i.e. 13 patients missing; [2] based on 99 patients, i.e. 1 patient missing; [3] based on 78 patients, i.e. 22 patients missing; [4] based on 80 patients, i.e. 20 patients missing

Table 2.8.8: Mean, Standard Deviation, And 95% Confidence Intervals For The Composite Recall, Paired Association, and Recognition Scores, On The New Test Of Memory, For The Patient Group (Controls Provided For Comparison)

	Patients (N=100)	Controls (N=85)
Verbal RCLL Total:		
mean (SD)	15.13 (4.47)[1]	17.18 (3.63)[5]
median (range)	15.00 (5-26)[1]	17.00 (9-25)[5]
95% confidence limits	14.17-16.09	16.39-17.97
Verbal PA Total:		
mean (SD)	12.31 (3.06)[1]	13.55 (2.65)[5]
median (range)	13.00 (4-17)[1]	14.00 (6-17)[5]
95% confidence limits	11.66-12.96	12.97-14.13
Verbal RECOG Total:		
mean (SD)	14.31 (2.34)[1]	15.93 (1.42)[5]
median (range)	15.00 (5-17)[1]	15.00 (10-17)[5]
95% confidence limits	13.81-14.81	15.62-16.24
Verbal Total:		
mean (SD)	41.75 (8.35)[1]	46.66 (6.20)[5]
median (range)	42.00 (19-59)[1]	46.00 (30-56)[5]
95% confidence limits	39.96-43.54	45.30-48.02
Spatial RCLL Total:		
mean (SD)	10.46 (4.24)[2]	13.29 (4.76)[6]
median (range)	10.50 (2-23)[2]	13.00 (5-25)[6]
95% confidence limits	9.50-11.42	12.19-14.39
Spatial PA Total:		
mean (SD)	5.56 (1.91)[3]	6.34 (2.51)[7]
median (range)	5.00 (2-9)[3]	6.00 (1-11)[7]
95% confidence limits	5.13-5.99	5.77-6.91

	Patients (N=100)	Controls (N=85)
Spatial RECOG Total:		
mean (SD)	9.93 (2.70)[3]	10.92 (2.43)[7]
median (range)	10.00 (3-15)[3]	11.00 (4-17)[7]
95% confidence limits	9.33-10.53	10.37-11.47
Spatial Total:		
mean (SD)	25.95 (6.75)[4]	30.73 (7.09)[6]
median (range)	25.00 (12-45)[4]	31.00 (17-51)[6]
95% confidence limits	24.42-27.48	29.12-32.34

RCLL = recall memory; PA = paired association; RECOG = recognition memory
[1] based on 87 patients, i.e. 13 patients missing; [2] based on 78 patients, i.e. 22 patients missing based on 80 patients, i.e. 20 patients missing; [4] based on 77 patients, i.e. 23 patients missing; [5] based on 83 subjects, i.e. 2 individuals missing; [6] based on 75 subjects, i.e. 10 individuals missing; [7] based on 77 subjects, i.e. 8 individuals missing

Table 2.8.9: Mean, Standard Deviation, And 95% Confidence Intervals For The Composite Scores On The New Test Of Memory, At The Task Familiarisation Stage, And The Two Difficulty Levels, For The Patient Group (Controls Provided For Comparison)

	Patients (N=100)	Controls (N=85)
TF Verbal Total:		
mean (SD)	9.55 (1.92)	10.34 (1.38)
median (range)	10.00 (2-12)	11.00 (6-12)
95% confidence limits	9.17-9.93	10.04-10.64
Set 1 Verbal Total:		
mean (SD)	12.62 (2.97)	13.75 (2.09)
median (range)	13.00 (6-19)	14.00 (9-18)
95% confidence limits	12.03-13.21	13.30-14.20
Set 2 Verbal Total:		
mean (SD)	19.23 (4.82)[1]	22.43 (4.21)[4]
median (range)	20.00 (6-28)[1]	23.00 (11-30)[4]
95% confidence limits	18.20-20.26	21.51-23.35

	Patients (N=100)	Controls (N=85)
TF Spatial Total:		
mean (SD)	6.41 (2.11)[2]	7.33 (1.90)[5]
median (range)	6.00 (2-11)[2]	7.00 (4-11)[5]
95% confidence limits	5.99-6.83	6.92-7.74
Set 1 Spatial Total:		
mean (SD)	7.77 (2.74)[2]	9.30 (2.82)[5]
median (range)	8.00 (1-14)[2]	9.00 (4-17)[5]
95% confidence limits	7.22-8.32	8.69-9.91
Set 2 Spatial Total:		
mean (SD)	11.01 (3.85)[3]	13.73 (4.13)[6]
median (range)	11.00 (2-22)[3]	14.00 (6-25)[6]
95% confidence limits	10.13-11.89	12.78-14.68
Overall Total:		
mean (SD)	67.68 (13.69)[3]	77.77 (11.45)[6]
median (range)	70.00 (31-103)[3]	78.00 (52-106)[6]
95% confidence limits	64.57-70.79	75.13-80.41

TF = Task Familiarisation

[1] based on 87 patients, i.e. 13 patients missing; [2] based on 99 patients, i.e. 1 patient missing; [3] based on 77 patients, i.e. 23 patients missing; [4] based on 83 subjects, i.e. 2 individuals missing; [5] based on 84 subjects, i.e. 1 individual missing; [6] based on 75 subjects, i.e. 10 individuals missing

Using Spearman's Rank Correlation Coefficient, it was found that age and sex did not correlate significantly with the verbal and spatial total scores, or the overall total on the New Test Of Memory (Table 2.8.10). However, NART-R IQ correlated positively with both composite scores, and the overall total of the new measure.

Table 2.8.10: A Correlation Matrix Of The Relationship Between Age, Sex, And NART-R IQ With The New Test Of Memory, For The Patient Group

	Age	Sex	NART-R IQ	New Test Verbal Total	New Test Spatial Total	New Test Overall Total
Age						
Sex	-0.11					
NART-R IQ	0.12	0.01				
New Test Verbal Total	0.09	-0.11	0.55 ***			
New Test Spatial Total	0.11	-0.02	0.53 ***	0.58 ***		
New Test Overall Total	0.10	-0.06	0.61 ***	0.90 ***	0.87 ***	

Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Tables 2.8.11 and 2.8.12 detail the correlations of the equivalent IQ on the spatial analogy section of the VESPAR with the verbal and spatial performance at the Task Familiarisation stage, and on Sets 1 and 2. It can be seen that intelligence does significantly affect performance on the New Test Of Memory during the initial phase and the two difficulty levels. This may be because some MS patients are aware that they have difficulty grasping a task, or that they have poor memory function, and therefore IQ influences performance. Patients with deteriorating intelligence may also be handicapped at learning the tasks.

Table 2.8.11: A Correlation Matrix Of The Relationship Between Equivalent IQ On the Spatial Analogy Section Of The VESPAR And Verbal Sections Of The New Test Of Memory, At The Task Familiarisation Stage And Two Difficulty Levels, For The Patient Group

	VESPAR IQ	New Test TF Verbal Total	New Test Set 1 Verbal Total	New Test Set 2 Verbal Total
VESPAR IQ				
New Test TF Verbal Total	0.48 ***			
New Test Set 1 Verbal Total	0.50 ***	0.63 ***		
New Test Set 2 Verbal Total	0.56 ***	0.54 ***	0.70 ***	

TF = Task Familiarisation
Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Table 2.8.12: A Correlation Matrix Of The Relationship Between Equivalent IQ On The Spatial Analogy Section Of The VESPAR And Spatial Sections Of The New Test Of Memory, At The Task Familiarisation Stage And Two Difficulty Levels, For The Patient Group

	VESPAR IQ	New Test TF Spatial Total	New Test Set 1 Spatial Total	New Test Set 2 Spatial Total
VESPAR IQ				
New Test TF Spatial Total	0.35 ***			
New Test Set 1 Spatial Total	0.43 ***	0.52 ***		
New Test Set 2 Spatial Total	0.49 ***	0.41 ***	0.50 ***	

TF = Task Familiarisation
Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

2.8.4 Reliability:

In the patient group, the internal reliability (Kline, 1993) of the New Test Of Memory was assessed using Cronbach's Alpha (Cronbach, 1951). This gave a value of 0.85 for the verbal sections, and, 0.74 for the spatial sections. These values are similar to those reported in the control sample, and again suggest that the test is a reliable, homogenous measure.

Tables 2.8.13 and 2.8.14 refer to the internal consistency (Kline, 1993) of the New Test Of Memory. Table 2.8.13 is the correlation matrix of verbal recall, paired association, and recognition, and spatial recall, paired association, and recognition sections, for the whole patient sample, while Table 2.8.14 is the correlations of Task Familiarisation, and Sets 1 and 2, for both verbal and spatial sections, again for the whole patient group. The correlations are of a strength expected for a measure which was designed to assess a variety of different types of memory and cover a wide range of abilities. This is because the various memory domains share a degree of general or non-specific memory competency.

2.8.5 Validity:

Informal feedback from the patients who participated in the study suggested that the New Test Of Memory possessed face validity (Bryman & Cramer, 1990), with subjects considering the test to measure memory, and not spontaneously reporting the stimuli or format to be inappropriate or irrelevant.

The construct validity (Streiner & Norman, 1989) of the new test was demonstrated using Spearman's Rank Correlation Coefficients between the verbal and spatial total scores of the New Test Of Memory and the WAIS-R vocabulary subtest,

and the spatial analogy section of the VESPAR (Table 2.8.15). These tasks were completed by all patients. It can be seen that the correlations are significant, suggesting that the tasks share 'g', but, as expected, they are moderate. (The general or 'g' factor was introduced by Spearman (1904; 1927), and refers to the single, common factor which all intellectual activities share.) The vocabulary subtest of the WAIS-R and the spatial analogy section of the VESPAR assess general verbal and spatial reasoning skills respectively, not memory specifically, thus it would be surprising if the correlations were stronger.

Table 2.8.13: A Correlation Matrix Of The Verbal And Spatial Sections Of The New Test Of Memory, For The Patient Group

	Verbal RCLL Total	Verbal PA Total	Verbal RECOG Total	Verbal Total	Spatial RCLL Total	Spatial PA Total	Spatial RECOG Total	Spatial Total
Verbal RCLL Total								
Verbal PA Total	0.60 ***							
Verbal RECOG Total	0.50 ***	0.55 ***						
Verbal Total	0.90 ***	0.84 ***	0.71 ***					
Spatial RCLL Total	0.45 ***	0.43 ***	0.32 **	0.47 ***				
Spatial PA Total	0.19	0.21	0.29 **	0.26 *	0.19			
Spatial RECOG Total	0.44 ***	0.41 ***	0.46 ***	0.51 ***	0.42 ***	0.32 **		
Spatial Total	0.52 ***	0.49 ***	0.48 ***	0.58 ***	0.83 ***	0.57 ***	0.75 ***	

RCLL = recall memory; PA = paired association; RECOG = recognition memory
Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Table 2.8.14: A Correlation Matrix Of The Verbal And Spatial Composite Scores Of The New Test Of Memory, At The Task Familiarisation Stage And The Two Levels Of Difficulty, For The Patient Group

	Verbal Total TF	Verbal Total Set 1	Verbal Total Set 2	Verbal Total	Spatial Total TF	Spatial Total Set 1	Spatial Total Set 2	Spatial Total
Verbal Total TF								
Verbal Total Set 1	0.63 ***							
Verbal Total Set 2	0.54 ***	0.70 ***						
Verbal Total	0.72 ***	0.87 ***	0.94 ***					
Spatial Total TF	0.27 **	0.28 **	0.36 ***	0.33 **				
Spatial Total Set 1	0.37 ***	0.41 ***	0.38 ***	0.41 ***	0.52 ***			
Spatial Total Set 2	0.39 ***	0.36 **	0.51 ***	0.49 ***	0.41 ***	0.50 ***		
Spatial Total	0.43 ***	0.48 ***	0.59 ***	0.58 ***	0.71 ***	0.80 ***	0.85 ***	

TF = Task Familiarisation; Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Table 2.8.15: A Correlation Matrix Of The New Test Of Memory With The WAIS-R Vocabulary Subtest And The VESPAR Spatial Analogy Section, For The Patient Group

	New Test Verbal	New Test Spatial	New Test Overall	WAIS-R Vocab.	VESPAR Spatial
New Test Verbal					
New Test Spatial	0.58 ***				
New Test Overall	0.90 ***	0.87 ***			
WAIS-R Vocab.	0.68 ***	0.53 ***	0.69 ***		
VESPAR Spatial	0.51 ***	0.47 ***	0.55 ***	0.48 ***	

Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Using the data from patients who completed the extensive neuropsychological battery, further construct validity (Streiner & Norman, 1989) was assessed. Table 2.8.16 shows the Spearman's Rank Correlation Coefficients of the verbal and spatial composite scores, and the overall total with the WAIS-R VIQ and VESPAR total, that is, for the three spatial sections. These correlations again demonstrate that the tests share 'g', and they are at a strength expected for the relationship between a test of memory and intelligence assessments.

Table 2.8.16: Correlations Matrix Of The Composite Scores Of The New Test Of Memory With Measures Of Verbal And Spatial Intelligence, For The Long Battery Patients

	Verbal Total	Spatial Total	Overall Total	WAIS-R VIQ	VESPAR Total
Verbal Total					
Spatial Total	0.59 ***				
Overall Total	0.89 ***	0.88 ***			
WAIS-R VIQ	0.62 ***	0.62 ***	0.67 ***		
VESPAR Total	0.53 ***	0.56 ***	0.56 ***	0.66 ***	

Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

The NRU patients completed a number of conventional memory assessments in addition to the New Test Of Memory. These data were used to construct a large correlation matrix, which allows the assessment of convergent and discriminant validity (Campbell & Fiske, 1959; Anastasi, 1976; Bryman & Cramer, 1990). Table 2.8.17 shows the Spearman's Rank Correlation Coefficients of the verbal and spatial recall, paired association, and recognition sections of the new measure, with the CVLT, RMTW, and subtests of the WMS-R. These correlations show the expected pattern of relationships among memory tasks. For example, the correlations are strong between the various conventional verbal memory measures and the verbal recall, paired association, recognition, and total variables of the new test. Likewise, the relationships between conventional visuo-spatial memory tasks and the spatial recall, paired association,

recognition, and total variables of the new measure are good. The correlations between verbal and visuo-spatial memory tasks, both conventional and new, are weaker.

Discriminant validity (Campbell & Fiske, 1959; Anastasi, 1976; Bryman & Cramer, 1990) is illustrated by the low and insignificant correlation between two measures which represent different concepts, and which are thought to be unrelated. Using the whole patient group and the overall total on the New Test Of Memory, it was found that performance on the new measure did not correlate with disease duration or disability as measured by the EDSS. This is not surprising, as the lack of relationship between cognitive function and both disease duration and disability has been reported in many studies. Likewise, level of anxiety and depression assessed by the HADS did not correlate with the overall total for the whole patient group. This finding is consistent with previous research, which has failed to find a significant relationship between depression and cognitive performance in MS, and suggests that any deficits in patient performance are not due to affective factors.

Table 2.8.17: A Correlation Matrix Of The New Test Of Memory With Conventional Memory Assessments For The Long Battery Patients

	Verbal RCLL Total	Verbal PA Total	Verbal RECOG Total	Verbal Total	Spatial RCLL Total	Spatial PA Total	Spatial RECOG Total	Spatial Total	CVLT trial 1	CVLT trial 5	CVLT total	RMTW
Verbal RCLL Total												
Verbal PA Total	0.56 ***											
Verbal RECOG Total	0.51 ***	0.55 ***										
Verbal Total	0.89 ***	0.83 ***	0.72 ***									
Spatial RCLL Total	0.56 ***	0.43 **	0.20	0.54 ***								
Spatial PA Total	0.13	0.13	0.32 *	0.21	0.09							
Spatial RECOG Total	0.33 *	0.31	0.44 **	0.44 **	0.53 ***	0.44 **						
Spatial Total	0.55 ***	0.41 **	0.41 **	0.59 ***	0.86 ***	0.49 **	0.79 ***					

	Verbal RCLL Total	Verbal PA Total	Verbal RECOG Total	Verbal Total	Spatial RCLL Total	Spatial PA Total	Spatial RECOG Total	Spatial Total	CVLT trial 1	CVLT trial 5	CVLT total	RMTW
CVLT trial 1	0.48 ***	0.47 ***	0.44 **	0.58 ***	0.52 ***	0.07	0.43 **	0.48 **				
CVLT trial 5	0.49 ***	0.53 ***	0.54 ***	0.64 ***	0.53 ***	0.43 **	0.64 ***	0.68 ***	0.63 ***			
CVLT total	0.53 ***	0.53 ***	0.47 ***	0.64 ***	0.62 ***	0.31	0.63 ***	0.69 ***	0.78 ***	0.92 ***		
RMTW	0.58 ***	0.54 ***	0.44 **	0.64 ***	0.65 ***	0.20	0.59 ***	0.71 ***	0.44 **	0.63 ***	0.60 ***	
WMS-R ve. pa	0.41 **	0.45 **	0.50 ***	0.53 ***	0.39 *	0.51 ***	0.53 ***	0.61 ***	0.56 ***	0.71 ***	0.65 ***	0.52 ***
WMS-R vi. pa	0.18	0.15	0.34 *	0.26	0.57 ***	0.37 *	0.60 ***	0.68 ***	0.40 **	0.63 ***	0.54 ***	0.56 ***
WMS-R fig. m	0.19	0.36 *	0.41 **	0.35 *	0.54 ***	0.39 *	0.46 **	0.65 ***	0.26	0.37 **	0.38 **	0.37 **
WMS-R rep. M	0.42 **	0.46 **	0.51 ***	0.55 ***	0.42 **	0.31	0.35 *	0.52 **	0.39 **	0.49 ***	0.56 ***	0.42 **
WMS-R ds	0.32 *	0.22	0.32 *	0.35 *	0.24	0.52 ***	0.48 **	0.45 **	0.25	0.42 **	0.42 **	0.34 *
WMS-R vs	0.50 ***	0.48 ***	0.40 **	0.59 ***	0.47 **	0.24	0.32 *	0.48 **	0.33 *	0.40 **	0.46 ***	0.48 ***

	WMS-R ve. pa	WMS-R vi. pa	WMS-R fig. m	WMS-R rep. m	WMS-R ds	WMS-R vs
WMS-R ve. pa						
WMS-R vi. pa	0.45 ***					
WMS-R fig. m	0.41 **	0.45 ***				
WMS-R rep. M	0.39 **	0.23	0.42 **			
WMS-R ds	0.36 **	0.32 *	0.09	0.36 *		
WMS-R vs	0.43 **	0.31 *	0.34 *	0.69 ***	0.61 ***	

RCLL = recall memory; PA = paired association; RECOG = recognition memory
ve. pa = verbal paired associates; vi pa = visual paired associates; fig. m = figural memory; rep. m = visual reproductions; ds = digit span; vs = visual memory span.
Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Table 2.8.18 illustrates the correlations for the long battery patients, with whom additional impairment and disability assessments were conducted. It can be seen that the verbal and spatial composite scores, and the overall total of the new test correlated weakly, in a negative direction, with the Functional Systems overall total, and moderately with the cerebral section of this measure (although the cerebral section is insensitive, providing only a crude measure of cognitive status). The composite scores of the new measure did not correlate with the bladder and bowel, pyramidal, sensory, or visual section of the Functional Systems, providing further evidence of the good discriminant validity of the New Test Of Memory. However, the significant negative correlations between the composite new test variables and the brain stem system, require explanation (the significant, negative correlation between the verbal total score and cerebellar system is considered relatively unimportant; it may be an artefact of the number of calculations being conducted, or it may be due to cerebellar dysarthria. However, the impact of cerebellar dysarthria on performance on the verbal sections of the new measure is likely to be minimal, as a spoken response is only required in the verbal recall sections; the paired association and recognition tasks providing an alternative response mode). Significant correlations with the FIM cognitive, a scale which is used to assess patients' everyday function, are also reported. This may suggest that the new measure assesses memory capabilities relevant to everyday life, and that there is a link with behavioural observations of competency in elementary, daily tasks.

Table 2.8.18: Correlations Of Clinical Variables With The Verbal, Spatial, And Overall Totals Of The New Test Of Memory, For The Long Battery Patients

	New Test Verbal Total	New Test Spatial Total	New Test Overall Total
Disease Duration	-0.072	-0.106	-0.170
EDSS	0.079	-0.143	-0.024
Functional Systems	-0.331 *	-0.417 **	-0.353 *
Functional Systems - bladder & bowel	-0.194	-0.214	-0.199
Functional Systems - brain stem	-0.336 *	-0.482 **	-0.414 **
Functional Systems - cerebral	-0.430 **	-0.508 ***	-0.453 **
Functional Systems - cerebellar	-0.436 **	-0.207	-0.319 *
Functional Systems - pyramidal	0.124	-0.159	-0.011
Functional Systems - sensory	0.233	0.076	0.210
Functional Systems - visual	-0.148	-0.266	-0.286
BARTHEL	0.094	0.238	0.163
FIM - motor	0.126	0.266	0.200
FIM - cognitive	0.377 **	0.500 **	0.467 **
FIM -cognitive (comprehension)	0.386 **	0.373 *	0.354 *
FIM - cognitive (expression)	0.446 **	0.349 *	0.357 *
FIM - cognitive (memory)	0.393 **	0.517 ***	0.500 **

	New Test Verbal Total	New Test Spatial Total	New Test Overall Total
FIM - cognitive (problem solving)	0.316 *	0.531 ***	0.454 **
FIM - cognitive (social interaction)	0.003	0.221	0.189
HADS	-0.130	-0.318	-0.255

Spearman's Rank Correlations; significance levels * p=0.05; ** p=0.01; *** p=0.001.

Factorial validity (Anastasi, 1976) for the New Test Of Memory can be found in Tables 2.8.19 and 2.8.20, which give details of the two factor solutions for the patient data, using a principal component analysis with varimax rotation. Following convention (Delis et al., 1987; Wechsler, 1987; Compton et al.,1992), composite scores, rather than individual items were entered as variables. It can be seen that for the Task Familiarisation stage, and the two levels of difficulty (Table 2.8.20), the solution identifies the strong verbal and spatial components previously demonstrated in the control data. However, the solution is less definite for the verbal and spatial recall, paired association, and recognition sections, with relatively high loadings for both factors on spatial recall and recognition (Table 2.8.19).

Table 2.8.19: Factor Analysis Of The Components Of The New Test Of Memory, For The Patient Group (Divided By Memory Domains)

Factor 1	**Verbal PA** 0.83
	Verbal RCLL 0.82
	Spatial RCLL 0.71
	Verbal RECOG 0.67
	Spatial RECOG 0.56
Factor 2	**Spatial PA** 0.94
	Spatial RECOG 0.53
	Spatial RCLL 0.40

RCLL = recall memory; PA = paired association; RECOG = recognition memory

Table 2.8.20: Factor Analysis Of The Components Of The New Test Of Memory, For The Patient Group (Divided At The Task Familiarisation Stage And The Two Difficulty Levels)

Factor 1	**TF Verbal Total** 0.84
	Set 1 Verbal Total 0.84
	Set 2 Verbal Total 0.79
Factor 2	**TF Spatial Total** 0.90
	Set 1 Spatial Total 0.61
	Set 2 Spatial Total 0.59

TF = Task Familiarisation

2.8.6 Range Of Scores:

Figures 2.8.1 to 2.8.15 show the performance of the patient group relative to that of the controls on the verbal and spatial recall, paired association, and recognition sections, and the verbal and spatial sets. It can be seen that, as has been demonstrated statistically, the patients consistently performed below that of the controls, with more patients achieving scores at the lower end of the available range. For the verbal and spatial paired association and recognition sections, the cumulative frequency distributions accommodate chance scores created by the multiple choice format.

Figure 2.8.1: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Verbal Recall Total Of The New Test Of Memory

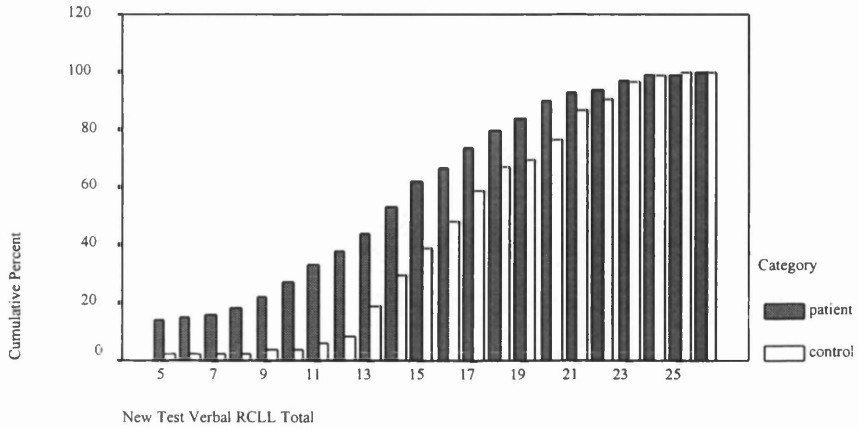


Figure 2.8.2: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Verbal Paired Association Total Of The New Test Of Memory

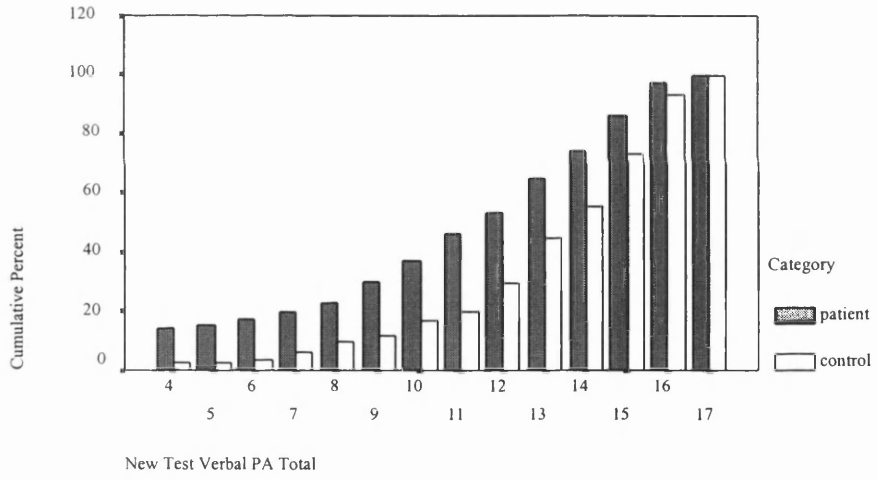


Figure 2.8.3: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Verbal Recognition Total Of The New Test Of Memory

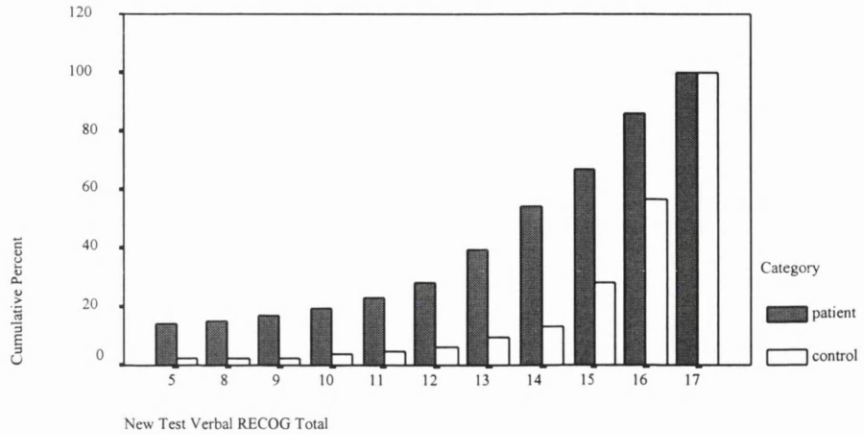


Figure 2.8.4: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Composite Verbal Total Of The New Test Of Memory

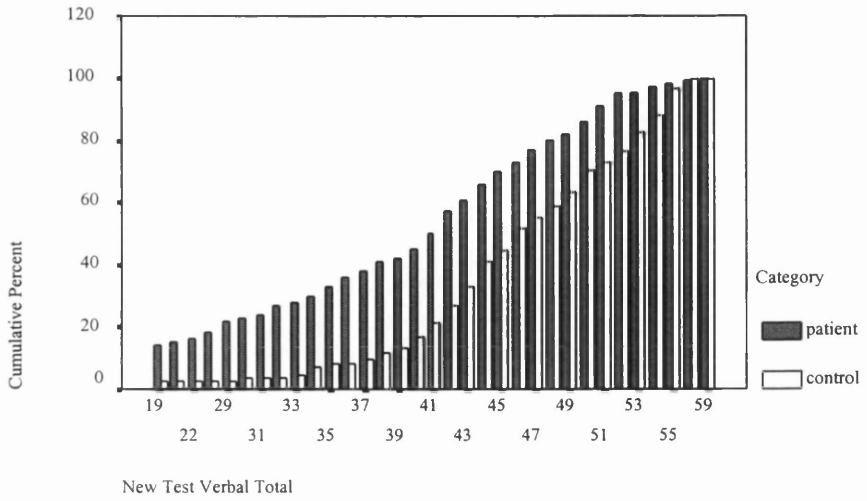


Figure 2.8.5: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Spatial Recall Total Of The New Of Memory

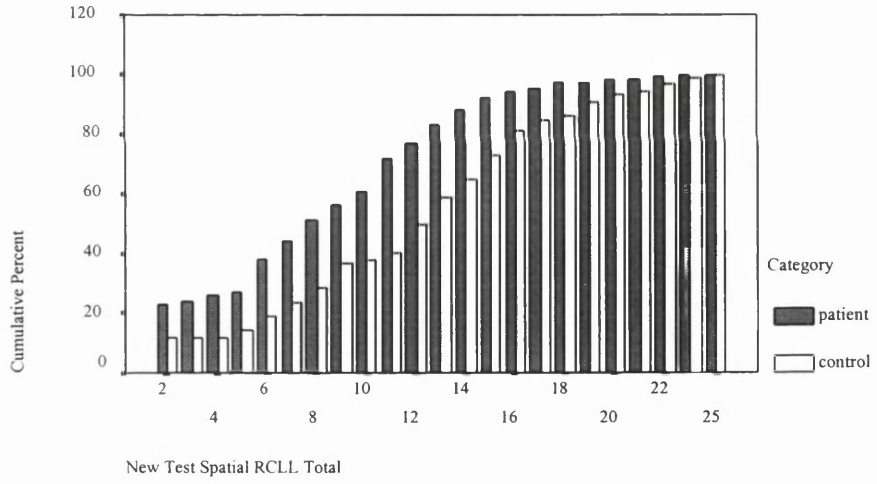


Figure 2.8.6: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Spatial Paired Association Total Of The New Test Of Memory

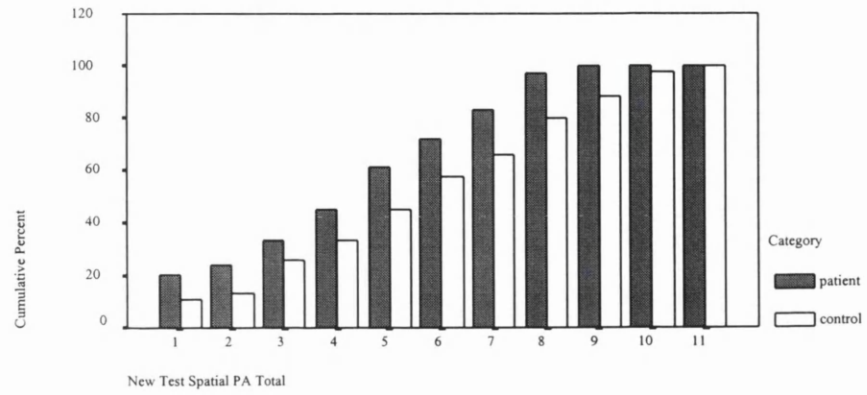


Figure 2.8.7: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Spatial Recognition Total Of The New Test Of Memory

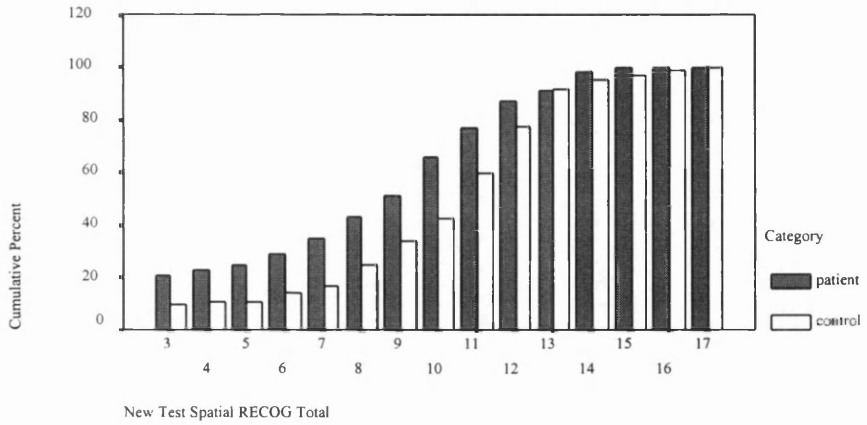


Figure 2.8.8: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Composite Spatial Total Of The New Test Of Memory

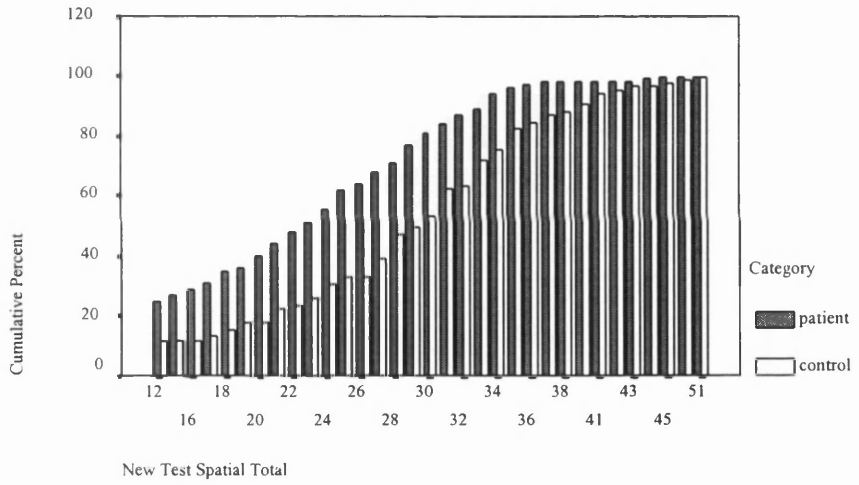


Figure 2.8.9: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Verbal Total Of The New Test Of Memory, At The Task Familiarisation Stage

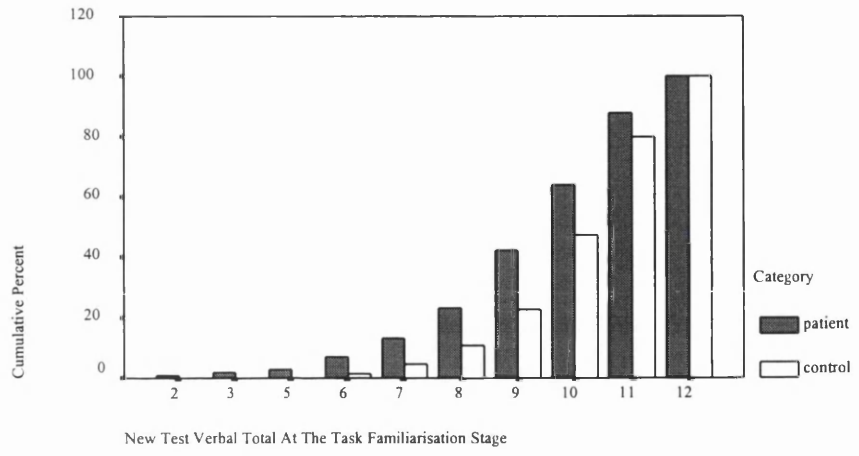


Figure 2.8.10: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Verbal Total Of Set 1 (The Easier Level), Of The New Test Of Memory

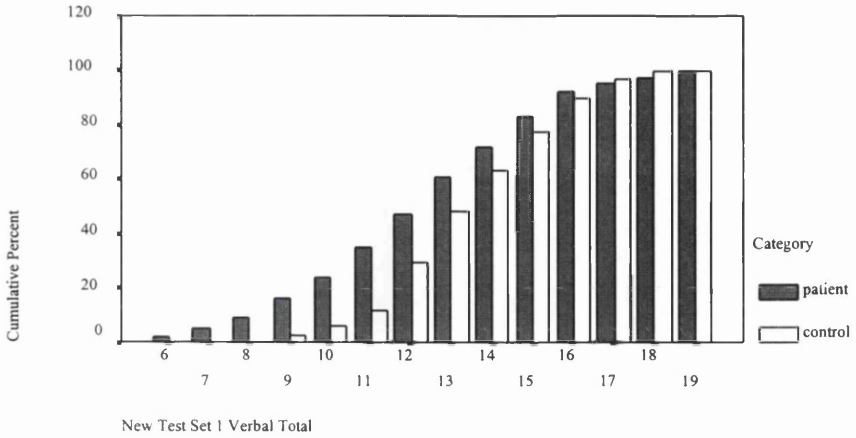


Figure 2.8.11: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Verbal Total Of Set 2 (The More Difficult Level) Of The New Test Of Memory

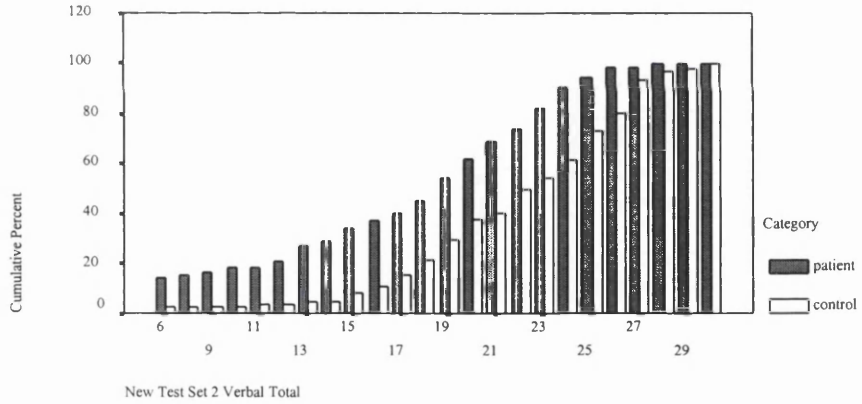


Figure 2.8.12: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Spatial Total Of The New Test Of Memory, At The Task Familiarisation Stage

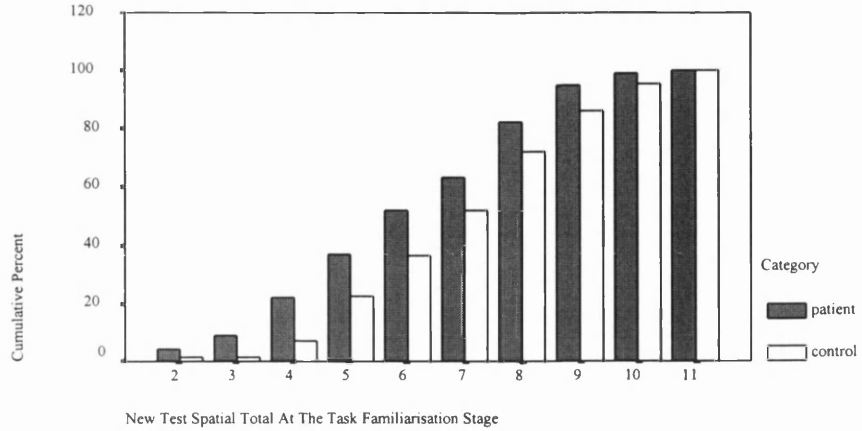


Figure 2.8.13: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Spatial Total Of Set 1 (The Easier Level) For The New Test Of Memory

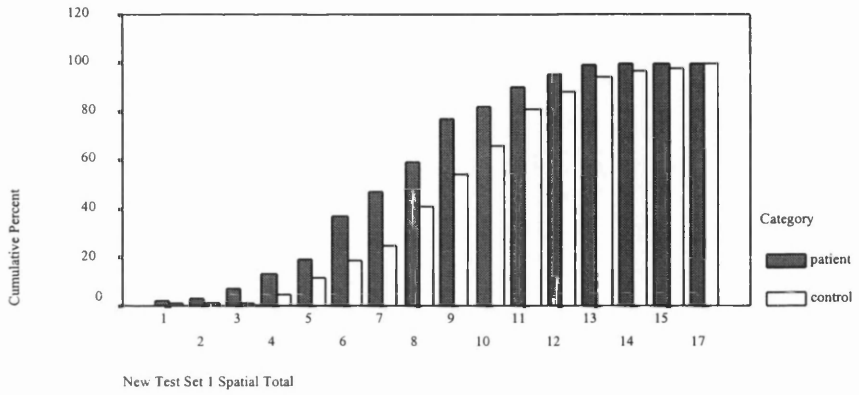


Figure 2.8.14: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Spatial Total Of Set 2 (The More Difficult Level) For The New Test Of Memory

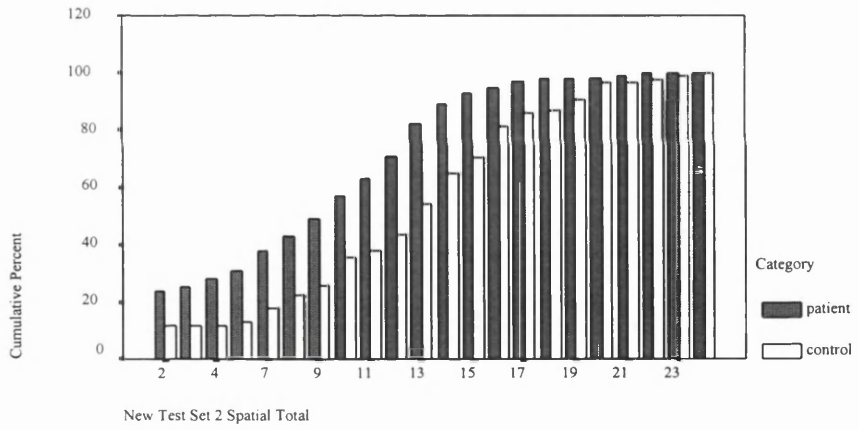
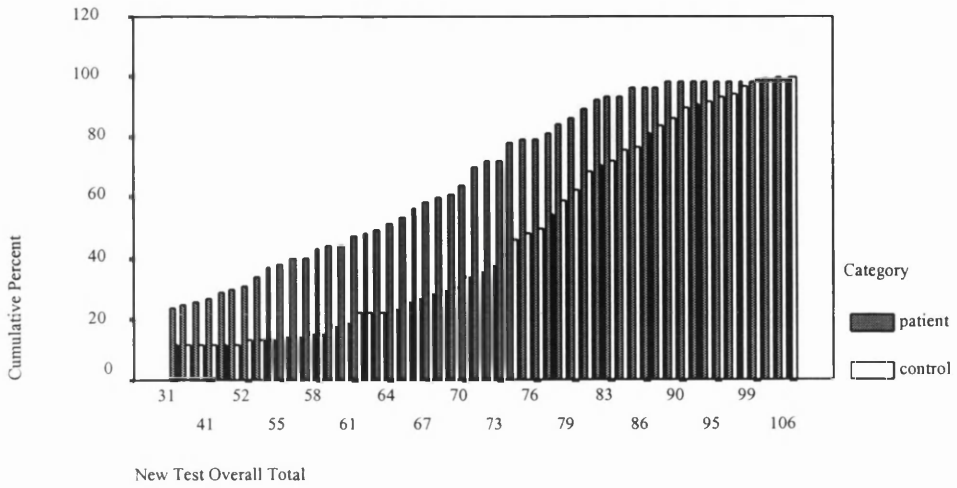


Figure 2.8.15: A Cumulative Frequency Distribution Showing The Performance Of Patients And Controls On The Overall Total Of The New Test Of Memory



As previously noted (Section 2.7.2), a number of patients declined to complete the verbal and/or spatial sections of Set 2 (the more difficult level). As there were no demographic, clinical, or cognitive (even on the Task Familiarisation stage, and Set 1 of the New Test Of Memory) differences between the subjects who did and did not undertake Set 2, and it was desirable to have maximum numbers to allow Set 2 verbal and spatial totals to be compared with those of the Task Familiarisation stage and Set 1 (the easier level), multiple regression was used to predict these missing scores.

Set 2 verbal total was predicted from NART-R IQ, Task Familiarisation verbal total, and Set 1 verbal total: $R^2 = 0.53$; significant F change = 0.001
Regression equation: - 2.211 + 0.05134 (NART-R IQ) + 0.488 (Task Familiarisation verbal total) + 0.878 (Set 1 verbal total)

Set 2 spatial total was predicted from NART-R IQ, Task Familiarisation spatial total, and Set 1 spatial total: $R^2 = 0.36$; significant F change = 0.001
Regression equation: -2.494 + 0.06494 (NART-R IQ) + 0.223 (Task Familiarisation spatial total) + 0.623 (Set 1 spatial total)

As expected, when the predicted and actual values of subjects who completed Set 2 were compared, the means were very similar. Thus for individuals who failed to complete any section of Set 2, the predicted values were substituted. This gave an adjusted Set 2 verbal total mean (SD) of 18.94 (4.77), median (range) 19.50 (6-28) and for Set 2 spatial total mean (SD) of 10.66 (3.65), median (range) 11.00 (2-22). Having substituted the missing values in Set 2, the overall verbal and spatial totals for these individuals could also be calculated. The overall verbal total mean (SD) 41.11 (8.59),

median (range) 42.00 (19-59), and overall spatial total mean (SD) 24.84 (7.12), median 25.00 (7-45).

2.8.7 Levels Of Difficulty:

Figures 2.8.16 to 2.8.21 illustrate the consistency of the difficulty levels; patients performing poorly at the Task Familiarisation stage, verbal or spatial total attained a low overall score, but the higher the score, the greater the composite total. This effect is also demonstrated at Sets 1 and 2, for both the verbal and spatial section, illustrating the robustness of the new measure.

Figure 2.8.16: A Scatter Plot Of The Percentage Correct On The Verbal Total At The Task Familiarisation Stage Against Overall Verbal Total, For The Patient Group

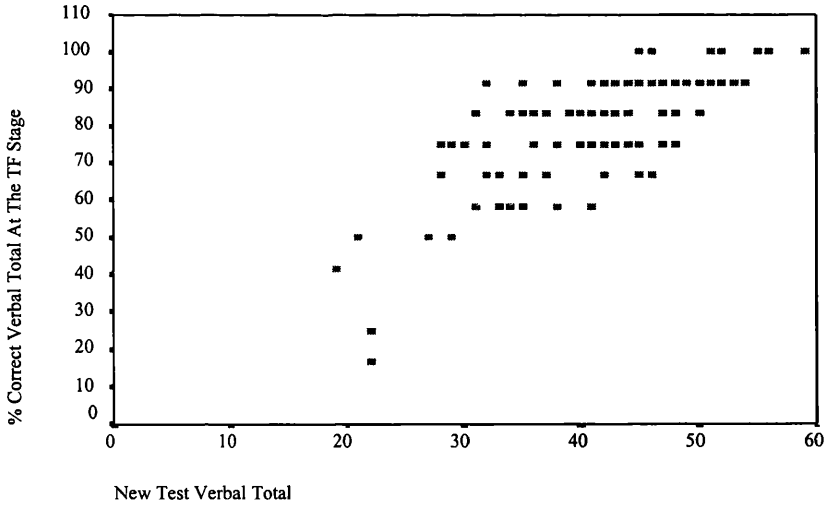


Figure 2.8.17: A Scatter Plot Of The Percentage Correct On The Verbal Total Of Set 1 (The Easier Level) Against Overall Verbal Total, For The Patient Group

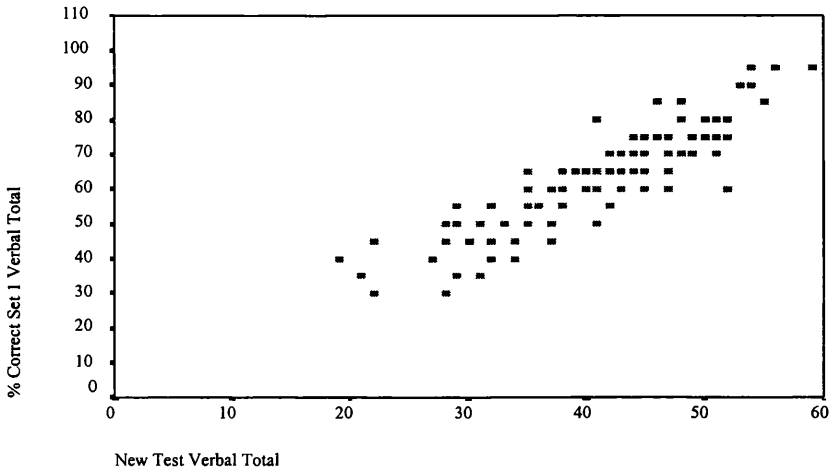


Figure 2.8.18: A Scatter Plot Of The Percentage Correct On The Verbal Total Of Set 2 (The More Difficult Level) Against Overall Verbal Total, For The Patient Group

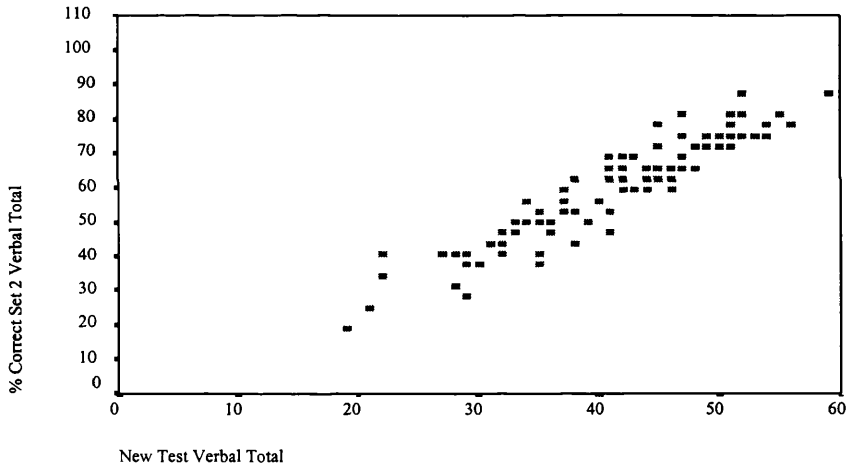


Figure 2.8.19: A Scatter Plot Of The Percentage Correct On The Spatial Total At The Task Familiarisation Stage Against Overall Spatial Total, For The Patient Group

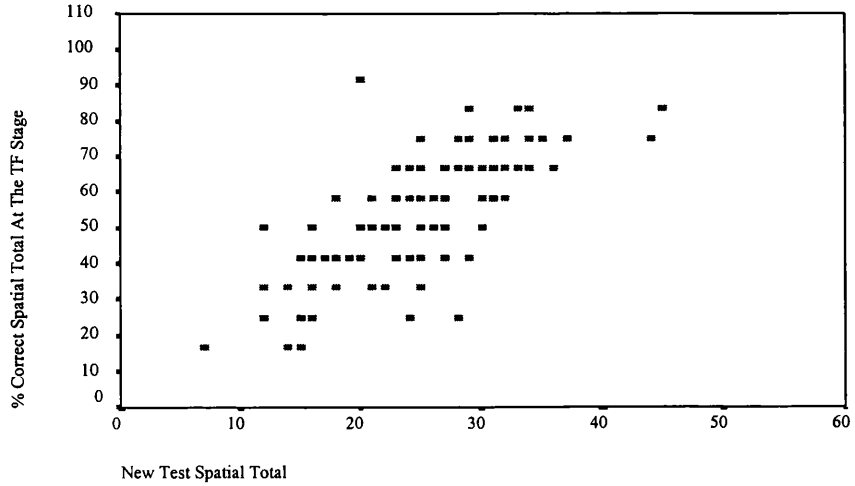


Figure 2.8.20: A Scatter Plot Of The Percentage Correct On The Spatial Total Of Set 1 (The Easier Level) Against Overall Spatial Total, For The Patient Group

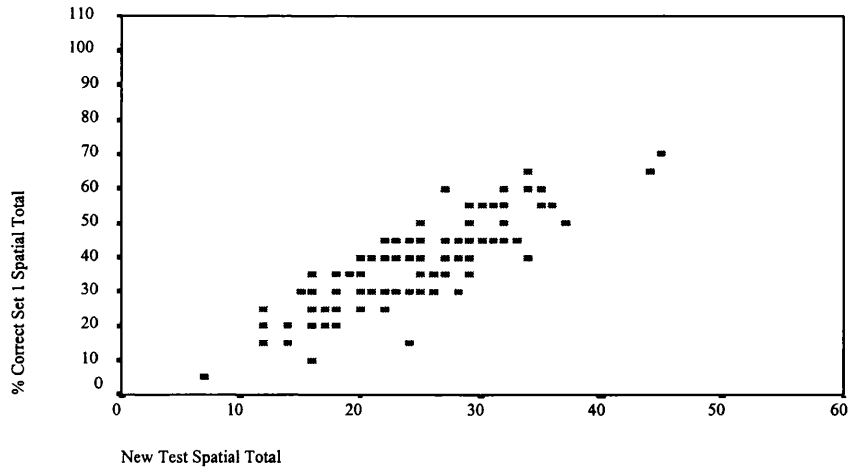
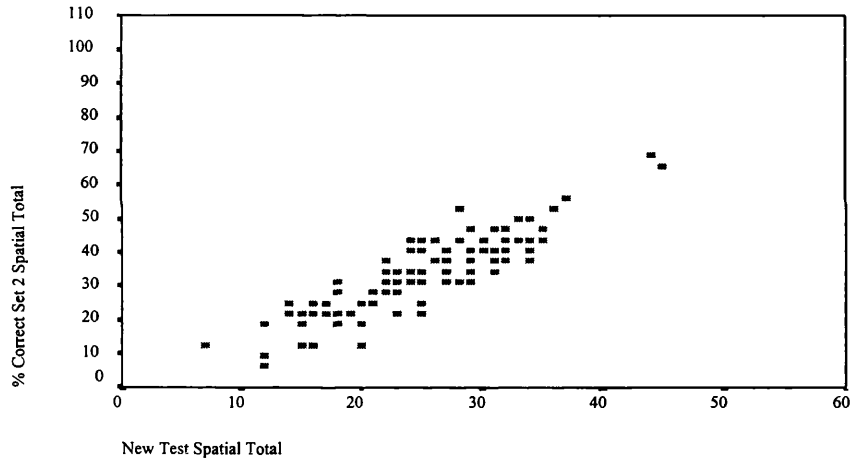


Figure 2.8.21: A Scatter Plot Of The Percentage Correct On The Spatial Total Of Set 2 (The More Difficult Level) Against Overall Spatial Total, For The Patient Group



2.8.8 Impairment And Percentiles:

The number of patients who scored at or below two SDs of the control group, and the percentage of patients at or below the 5th, 25th, and 50th percentiles, were calculated for the verbal and spatial recall, paired association, and recognition sections. These are shown in Table 2.8.21. Using the impairment criterion of at or below two SDs of the age group control mean, it can be seen that more patients were classed as impaired on the verbal subtests of the New Test Of Memory than on the spatial sections.

However, when different cut-offs were used to categorise patients as impaired, namely, the 5th, 25th and 50th percentile of age group controls, on the domains examined by the New Test Of Memory, this trend was less pronounced. Further analyses revealed that both verbal and spatial memory dysfunction appeared to show a strong general processing component, with several patients failing more than one domain, for example, recall and recognition memory. This suggested shared deficits across the types of verbal or spatial memory. This is illustrated in Figure 2.8.22, where the cut-off of the 25th percentile has been used as an example.

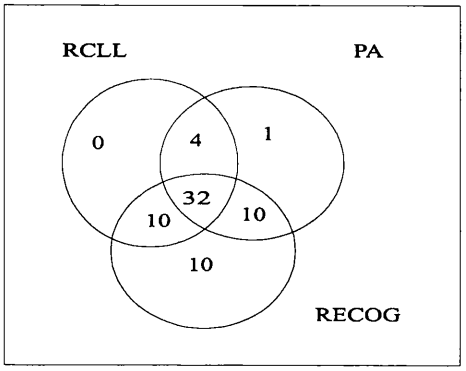
Table 2.8.21: The Number Of Patients Scoring At Or Below Two SDs Of The Age Group Control Mean, And The Percentage Of Patients Scoring At Or Below The 5th, 25th, and 50th Percentile, On The New Test Of Memory

	Number (%) of patients at or below 2 SDs	Percentage of patients at or below control group percentiles:		
		5	25	50
[1]Verbal RCLL Total	17 (19.5%)	24.1	52.9	70.1
[1]Verbal PA Total	11 (12.6%)	8.0	54.0	72.4
[1]Verbal RECOG Total	22 (25.3%)	17.2	71.3	88.5
Verbal Total	23 (23.0%)	25.0	64.0	72.0
[2]Spatial RCLL Total	4 (5.1%)	23.1	46.2	79.5
[3]Spatial PA Total	2 (2.5%)	12.5	42.5	70.0
[3]Spatial RECOG Total	9 (11.3%)	15.0	51.3	83.8
[4]Spatial Total	15 (15.2%)	28.3	57.6	72.7

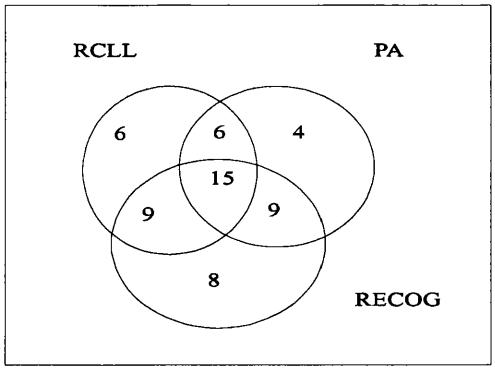
RCLL = recall memory; PA = paired association; RECOG = recognition memory
[1] data based on 87 patients, i.e. 13 patients missing
[2] data based on 78 patients, i.e. 22 patients missing
[3] data based on 80 patients, i.e. 20 patients missing
[4] data based on 99 patients, i.e. 1 patient missing

Figure 2.8.22: Venn Diagrams Showing The Number Of Patients Who Were Classed As Impaired On The Different Sections Of The New Test Of Memory, Applying The Cut-Off Of At Or Below The 25th Percentile Of The Controls For The Relevant Age Group

VERBAL



SPATIAL



RCLL = recall memory; PA = paired association; RECOG = recognition memory

Of those patients classed as impaired (using the criteria of at or below two SDs of the age group control mean) on the verbal total score of the New Test Of Memory, 17 individuals were impaired on one or more verbal sections: six individuals were impaired on all verbal sections, two patients were impaired on the verbal paired association and recognition sections, five patients were impaired on the verbal recall and recognition sections, two subjects failed only the verbal recall section, one patient just the verbal paired association section, and another only the verbal recognition section. For the spatial total score, seven subjects were categorised as impaired overall and failed one or more of the spatial recall, paired association, and recognition sections: one patient was impaired on both the spatial recall and recognition sections, and another on the spatial paired association, and recognition sections, one patient failed spatial recall alone, one subject was impaired on just the spatial paired association section, and three individuals were only impaired on the spatial recognition section.

Using the criteria of at or below two SDs of the age group control mean: nine patients were classed as impaired on both the verbal and spatial total scores, three patients failed the verbal and the spatial recall sections, one subject was impaired on

both paired association sections, and four patients failed the verbal and spatial recognition sections. Table 2.8.22 shows the number of patients who failed both the verbal and spatial sections of each memory domain, and the verbal and spatial totals, using the 5th, 25th, and 50th percentile as the cut-offs. It can be seen that even at the 5th percentile, at least 20% of patients were impaired on both verbal and spatial sections of each memory domain. This again suggested that memory dysfunction in MS seems to have a strong, general processing component, with patients failing memory tasks in both the verbal and spatial modalities.

Table 2.8.22: The Number Of Patients Who Scored At Or Below The 5th, 25th, and 50th Percentile Of The Age Group Controls On The New Test Of Memory

		No. of patients who fell below stated cut-off for each section **Verbal:Spatial**	No. of patients who were classed as failing both sections
5th percentile	RCLL sections[1]	19:18	10
	PA sections[2]	6:10	2
	RECOG sections[2]	14:12	5
	Total[3]	25:28	15
25th percentile	RCLL sections[1]	42:36	29
	PA sections[2]	44:34	22
	RECOG sections[2]	57:41	36
	Total[3]	63:57	47
50th percentile	RCLL sections[1]	55:62	45
	PA sections[2]	60:56	43
	RECOG sections[2]	71:67	62
	Total[3]	71:72	59

RCLL = recall memory; PA = paired association; RECOG = recognition memory
Only includes subjects for whom both verbal and spatial values were available
[1] data based on 78 patients, i.e. 22 patients missing; [2] data based on 80 patients, i.e. 20 patients missing;
[3] data based on 99 patients, i.e. 1 patient missing

Using pass or fail (where failure was taken as scoring at or below two SDs of the age group control mean) on the verbal or spatial total as the grouping variable, and the Mann-Whitney test (with a Bonferroni Correction for multiple tests, Bland & Altman, 1995), there were no significant differences between the clinical characteristics of the patients classed as impaired or intact. In the comparison of demographic characteristics, the only significant difference between impaired and intact individuals occurred in the time to complete the NHPT with the dominant hand, which was significantly greater in the impaired patients. However, of those classed as impaired, five patients were unable to complete the task due to such poor manual dexterity, similarly, of those intact, nine patients were unable to attempt the NHPT for the same reason. This suggests little difference in the upper limb function of the two patient groups.

Table 2.8.23 shows that for both the verbal and spatial sections, the number of patients classed as impaired increases with the difficulty level, that is, from Set 1 to Set 2. Twenty two patients were impaired on the verbal total score and were classed as impaired on one or both of the verbal Sets, and 11 patients were categorised as impaired overall on the spatial total score, and were impaired on one or both of the spatial Sets.

Table 2.8.23: The Number Of Patients Scoring At Or Below Two SDs Of The Age Group Control Mean On The New Test Of Memory

	Number of patients at or below 2 SDs
Verbal Total Set 1	16
Verbal Total Set 2	19
[1]Spatial Total Set 1	7
[1]Spatial Total Set 2	13

[1] data based on 99 patients, i.e. 1 patient missing

2.8.9 Degree Of Impairment:

To assess the degree of memory impairment using the New Test Of Memory, an impairment index was constructed dependent on the number of SDs below the age group control mean the patient's score fell, hence, the lower the actual score, the greater the impairment index. This system was applied to the verbal and spatial recall, paired association, and recognition totals. Table 2.8.24 shows the range of impairment, and the number of patients at each point of the impairment index for the verbal and spatial sections of the new measure.

Table 2.8.25 details the range of impairment indices on the New Test Of Memory, when compared with the decrease in IQ from the premorbid, optimum level (NART-R IQ minus predicted IQ on the spatial analogy subtest of the VESPAR). It can be seen that the MS patients with intact intelligence demonstrated a range in the severity of their memory impairments. Likewise, patients with marked IQ deficiencies also exhibited varying levels of memory defects. These findings support those noted in Section 2.8.3, that, although performance on the New Test Of Memory correlates with intelligence, the test is not solely driven by IQ. It also illustrates the heterogeneity of cognitive dysfunction in patients with MS.

Table 2.8.24: The Range Of Impairment Indices And The Number Of Patients At Each Point Of The Index

	Impairment Indices:					
	0	1	2	3	4	5+
Verbal RCLL total	54	16	13	4	0	0
Verbal PA Total	61	15	7	4	0	0
Verbal RECOG Total	46	19	9	8	2	3
Verbal Total	56	21	14	7	1	1
Spatial RCLL Total	48	26	4	0	0	0
Spatial PA Total	63	15	2	0	0	0
Spatial RECOG Total	55	16	6	3	0	0
Spatial Total	57	27	12	3	0	0

RCLL = recall memory; PA = paired association; RECOG = recognition memory

Table 2.8.25: The Range Of Impairment Indices On The New Test Of Memory, Compared With Frequency Of IQ Deficit

	New Test Of Memory Verbal Total Impairment Indices:					
	0	1	2	3	4	5+
No change in IQ	17	11	5	4		
Fall in IQ 1-10 points	19	6	4	2	0	1
Fall in IQ 11-20 points	15	2	5	1		
Fall in IQ 21-30 points	2	1				
	New Test Of Memory Spatial Total Impairment Indices:					
	0	1	2	3	4	5+
No change in IQ	18	14	5			
Fall in IQ 1-10 points	18	9	3	2		
Fall in IQ 11-20 points	17	3	3			
Fall in IQ 21-30 points	2	0	1			

2.8.10 Visual Acuity And Manual Dexterity Considerations:

One of the aims of the New Test Of Memory was that it should be an appropriate assessment for patients with poor manual dexterity and visual acuity. The visual acuity of the patients varied greatly, from those with perfect vision to those severely compromised. However, all subjects (except one individual who has been discussed previously; Section 2.7.2) were able to attempt the different sections of the new measure, suggesting that ability to perform the tasks was not affected by visual capability. (It must be noted that the New Test Of Memory was not applicable to the two patients who were registered as partially sighted and therefore excluded from the study, Section 2.7.2) Likewise, a number of MS patients demonstrated limited manual dexterity, being unable to complete the NHPT with either their dominant (N=14) or non dominant (N=18) hand. However, all patients (except one individual who has been discussed previously; Section 2.7.2) were able to complete the study phase of the Task Familiarisation and Set 1 (the easier level) spatial recall, demonstrating physical capability to complete the task. The fact that all patients were able to copy the position of the bar within the 5cm zone detailed in Section 2.2.3, completing the manoeuvre without help from the examiner, suggests that the assessment did not automatically penalise them for their compromised upper limb functioning. In order to examine this claim statistically, Spearman's Rank Correlation Coefficient was used to determine whether poor manual dexterity had a significant impact on copying performance on the spatial recall sections. For the purposes of these calculations, patients who were unable to attempt the NHPT were given the time of the patient who took the longest to complete the task, with the dominant and non dominant hand respectively. There were no significant correlations between time to complete the NHPT with dominant or non dominant hand and performance on the study phases of the New Test Of Memory. This

again suggests that the physical capabilities of the recall sections did not have an effect on accuracy of copying the position of the bar. Additional analysis using a Mann-Whitney test with Bonferroni Correction for multiple tests (Bland & Altman, 1995), demonstrated that there were no significant differences in the copying ability of those who were classed as impaired on the NHPT (where impairment was categorised as taking longer than two SDs above the age group control mean, with dominant and non dominant hand respectively). Further support for the usefulness of the New Test Of Memory in the assessment of patients with limited manual dexterity was provided by the NRU patients, who exhibited the same pattern of results as that detailed above. These patients also completed the visual reproduction subtest of the WMS-R, which has been criticised as an inappropriate memory assessment for severely physically disabled subjects. Spearman's Rank Correlation Coefficient demonstrated a weakly significant negative relationship between performance on the NHPT with the dominant hand and scores on this section ($r = -0.29$; $p = 0.05$). As ability on the visual reproduction subtest of the WMS-R did not correlate with EDSS, a measure of more general physical disability, and performance on the test phases of the spatial recall sections of the new measure did not give significant correlations with time to complete the NHPT, it was considered that the New Test Of Memory may be a purer measure of spatial recall memory than those currently available, and one which is less likely to penalise patients for limited motor skills.

2.9 THE PATIENT SAMPLE: DISCUSSION

2.9.1 The New Test Of Memory:

The New Test Of Memory was devised to provide a reliable and valid, matched, verbal and spatial assessment of explicit recent memory, which graded ability. Furthermore, the recall memory, paired association, and recognition memory tasks were designed to place minimal demands on sensori-motor skills and cognitive functions aside from memory. Analyses of the data from the validation sample suggest that these requirements have been met.

2.9.1.1 Applicability:

The patient group comprised individuals with varying levels of physical disability, from the mildly affected to the severely disabled. In addition, the patients exhibited a range of neuropsychological deficits, from those with no cognitive dysfunction to those with marked deficiencies. That all patients (except one who has been previously discussed, Section 2.7.2), were able to attempt each verbal and spatial section of the Task Familiarisation stage and Set 1 of the New Test Of Memory, demonstrates the applicability of the assessment tool for examining memory function in a patient group, who may exhibit compromised sensori-motor skills and coincident cognitive dysfunction. It also suggests that the format, imposed by the requirements of applicability for the most physically and cognitively impaired patients, did not render the test inappropriate for assessing memory in less disabled or intact individuals.

That patient performance on the new measure did not correlate significantly with level of disability as assessed by the EDSS suggests that the degree of physical

disability did not have a significant impact on cognitive test performance. It also provides further support for the appropriateness of the New Test Of Memory for the assessment of memory in a patient group, who may exhibit marked physical disability. In the long battery patient group, performance on the New Test Of Memory did not correlate significantly with scores on the visual system section of the Functional Systems. This suggests that visual disturbances did not affect memory test performance, indicating the appropriateness of the new measure for the assessment of memory in patients who may have limited visual acuity.

The format for the verbal and spatial recall, paired association, and recognition sections at the Task Familiarisation stage, and for Sets 1 and 2, comprised a study phase followed by testing. The study phase of each section afforded the opportunity to ensure that the physical requirements of each task were not beyond the capabilities of the patient. It also addressed issues concerning the necessity for supplementary cognitive skills in the accurate assessment of memory function. For all verbal sections, where the high frequency words were presented visually, asking the subject to make a decision about the target items ("is this a word you would use everyday?" or "are these words you would use everyday?"), initially attempted to confirm that he or she was able to see the items. In addition, the presentation mode and requirement to respond to the question ensured that the subject had attended to the stimuli. This attempted to reduce the effects of normal variation and deficits in attention. In the recall memory test phase, the use of high frequency items and the generous timing endeavoured to facilitate the task demands for subjects with acquired language dysfunction. For the test phases of the paired association and recognition sections, the visual presentation of items, which allowed the subject to indicate his or her answers by pointing or by speaking, minimised any handicaps imposed by more specific response demands.

In the spatial recall sections, the subject was first required to copy the position of the bar for each item before any assessment of memory was made. This ensured that he or she was able to see the stimuli, and was physically able to position the bar, prior to testing memory. (None of the subjects in the current study were unable to manoeuvre the bar) It also acted as a screen, attempting to identify subjects with gross perceptual and/or motor dysfunction. In the spatial paired association and recognition memory study phases, the subject was again presented with the items visually, and asked to make a decision about the stimuli ("are these shapes you could easily copy?"). This attempted to accommodate patients with attentional deficiencies. The simple structure of the items also endeavoured to minimise the difficulties for patients with perceptual dysfunction or peripheral visual disturbances. In the test phases, the visual presentation mode again gave the subject the opportunity to indicate his or her answers by pointing or by speaking.

Additional analyses of the patient study and test phase data for the spatial recall sections revealed that ability to copy the bar position was not related to patient performance on the manual dexterity task (NHPT). This reinforced the appropriateness of the assessment for patients with restricted sensori-motor skills. The long battery patients demonstrated a significant negative correlation between time to complete the NHPT with the dominant hand and performance on the visual reproduction subtest of the WMS-R, which requires subjects to draw from memory. Performance on the same section of the WMS-R did not correlate with overall disability as measured by the EDSS, and this suggests that the specific manual dexterity difficulties of the patients were perhaps partially responsible for their poor performance on the memory task. The absence of a correlation between the NHPT and the recall memory test scores on the

New Test Of Memory suggests that the new measure was not adversely affected by patients' restricted upper limb function.

Thus, the New Test Of Memory has been demonstrated to be applicable for all patients in the validation sample. The data suggest that the task demands of the measure are appropriate for the assessment of verbal and spatial recall memory, paired association, and recognition memory across the spectrum of ability. Various analyses have demonstrated that good manual dexterity and visual acuity are not prerequisites for efficient memory performance on the new test. It has also been shown that compromised sensori-motor skills and level of physical disability do not have a significant impact on cognitive performance on the New Test Of Memory. The new measure appears to accommodate individuals with coincident cognitive deficits, such as perceptual dysfunction, attentional deficiencies, or language difficulties. It attempts to assess memory independent of such confounding factors. However, this is an aspect of the New Test Of Memory which requires confirmation by a further study.

2.9.1.2 Psychometric Properties:

The validation sample demonstrated a wide range of scores on all sections of the New Test Of Memory (Tables 2.8.7 to 2.8.9; Figures 2.8.1 to 2.8.15), which supports the suggestion that the new measure grades ability across the target spectrum, and has the potential to be sensitive to change, although this has yet to be proven.

The internal reliability (Kline, 1993) of the New Test was demonstrated by the high values for Cronbach's Alpha (Section 2.8.4), indicating that the items comprising the assessment tool measure the same concept. The New Test Of Memory also showed good internal consistency, with moderate correlations between the various memory

domains of the new measure (Table 2.8.13), and between the Task Familiarisation stage and the two levels of difficulty (Table 2.8.14). These findings suggest that the sections of the new measure, like conventional memory tasks, in part assess general memory capability, which is not specific to a particular domain. These data, therefore, indicate that the New Test Of Memory is a reliable, homogeneous measure.

Validity (i.e. the extent to which the new memory test assesses the concept it was intended to measure; Bryman & Cramer, 1990), was also examined using the patient data. The face validity (Anastasi, 1976) of the new measure was supported as none of the patient group spontaneously commented that the tasks comprising the new assessment were inappropriate, irrelevant, or that the test did not measure memory.

Construct validity (Anastasi, 1976; Bryman & Cramer, 1990) of the New Test Of Memory was demonstrated by the moderate correlations of the new assessment with tests of general verbal ability and spatial reasoning skills (Table 2.8.15 & 2.8.16), suggesting that the tasks share 'g'. The moderate strength of the correlations is appropriate, as the WAIS-R and VESPAR do not measure memory, but more general intelligence or reasoning skills.

Using the data from the patients who completed the long battery of neuropsychological tasks, the correlation matrix of composite variables of the new measure with conventional memory tasks (Table 2.8.17), showed the New Test's convergent and discriminant validity (Campbell & Fiske, 1959). The matrix illustrates the relationships between verbal and visuo-spatial memory tasks currently used in clinical practice, and the verbal and spatial sections of the New Test Of Memory. As expected, correlations between memory measures within the same modality, that is, verbal or visuo-spatial, with the relevant composite scores of the new measure, tend to be higher than those from the opposing modality.

Discriminant validity (Campbell & Fiske, 1959; Anastasi, 1976; Bryman & Cramer, 1990), was also demonstrated by the new test. Correlations between performance on the new measure and clinical characteristics were weak and insignificant (Table 2.8.18). Performance on the New Test Of Memory did not correlate significantly with disease duration, level of disability, measured using the EDSS, Barthel or the motor sections of the FIM, or level of depression, according to the HADS. These findings are consistent with the literature (Sections 1.1.2 & 1.1.3). That performance on the New Test Of Memory did not correlate with some aspects of the Functional Systems, namely, pyramidal, visual, bladder and bowel, or sensory systems sections (Table 2.8.18), further illustrated the discriminant validity of the new measure, suggesting that the test is specific to memory and is not a general index of disease severity.

Lesion and functional imaging studies have demonstrated the involvement of anatomically distinct regions in different memory systems. Factor analysis was used to investigate whether these discrete areas could be identified in the MS sample. The factorial validity (Anastasi, 1976) of the New Test Of Memory was demonstrated by the two factor analyses, which revealed a clear verbal/spatial split for the Task Familiarisation stage and two levels of difficulty (Table 2.8.20), but only a partial split for the memory domains, as spatial recall and recognition loaded highly on both factors (Table 2.8.19). These findings may suggest that the individual tasks are not discriminatory in the patient group. However, as the relevant factor analysis of the control sample demonstrated a clear verbal/spatial split, this seems unlikely. It is more probable that there is limited fractionation of memory abilities in the patient group. This may be because, contrary to other neurological populations (e.g. those with amnesic syndrome), the associated cognitive processes which are necessary for efficient memory

functioning, and/or the actual memory processes, are often affected in MS. Intact memory processing initially entails the association of information from a variety of different brain regions. The hippocampus receives extrinsic inputs, via the entorhinal cortex and the parahippocampal gyrus, from many areas of the cerebral association cortex (Rolls, 1995). There are also subcortical cholinergic inputs from the septum. The hippocampus in turn projects back, via the subiculm, entorhinal cortex, and parahippocampal gyrus, to the cerebral cortical areas from which it receives inputs, as well as the subcortical areas such as the mamillary bodies (Rolls, 1995). This suggests that explicit recent memory is achieved by a sequence of stages, each of which involves a major set of input axons connecting, via a matrix of synapses, with the output neurons (Rolls, 1995). The encoding, storage, and retrieval of information therefore utilises distributed neural networks. In MS, demyelination may affect the neural pathways linking various brain regions, potentially impacting on the processes that may be involved in all memory functions. It may also disrupt the distributed networks used to encode, store, and retrieve information; once more preventing efficient memory processing in both verbal and/or spatial domains. (see Section 2.9.2.5).

Thus, the data from the validation sample begins to establish the validity of the New Test Of Memory, suggesting that the new measure does in fact assesses memory function in patients with MS. The analyses of the psychometric properties of the New Test Of Memory have indicated that it is reliable and valid, allowing the findings in the patient group to be examined with confidence, and permitting detailed discussion of the implications of its results.

2.9.2 Discussion Of Findings:

2.9.2.1 Sample:

The validation sample comprised 100 patients with MS, who appeared representative of the heterogeneous MS population. The group reflected the well documented higher incidence of the disease among females than males (Confavreux et al., 1980), with clinical features which spanned a broad range of disease durations (less than one year to 31 years), disease types (RR, PP, SP, and benign), and levels of disability (EDSS 1.5 to 9.0). The mean age at disease diagnosis (34.93 years), is not directly comparable to the mean age of disease onset typically reported in natural history studies (Confavreux et al., 1980, 31.31 years; Weinshenker et al., 1989, 30.5 years). This supposed discrepancy is explained when it is emphasised that the current study used age at diagnosis of MS, which is, by definition, later than the onset of symptoms. Given that clinical details were retrieved retrospectively from the medical records, that is, this aspect of the study was not prospective, it was considered more accurate to take note of the date of diagnosis, rather than an inevitably anecdotal account of the onset of symptoms. The MS patient group demonstrated a variety of disease types. However, the group was taken together as one cohort for the data analyses of the current study. This was because on subdivision, the different disease groups comprised relatively small numbers, and, when comparing patients with varying subtypes of MS, the inevitable differences in their level of physical disability and disease duration must be controlled (Thompson, 1998).

The comparison of the demographic details of the patients, relative to the healthy controls, indicated that the two groups differed only in terms of their occupational category (in that controls were more likely to be employed), manual dexterity (controls

took less time to complete the NHPT with either hand), and level of depression (controls were less depressed according to the HADS). These findings were considered unsurprising for patients with a chronic neurological disease. Only eight per cent of the patients achieved a score consistent with definite depression (Zigmond & Snaith, 1983), hence affective factors were unlikely to bias cognitive test performance negatively. In addition, premorbid IQ, estimated using the NART-R, was not significantly different between patients and controls. These findings, therefore, allow comparisons and evaluations based on the control series to be treated with confidence.

MS patients were recruited from both inpatient and outpatient settings, and this attempted to reduce the bias, often unavoidable in studies conducted at established research centres, where the patient sample tends to be preselected, with subjects exhibiting greater physical disability, or more active disease, than community-based individuals (Nelson et al., 1988). Despite recruiting patients from a teaching hospital, the majority of outpatient appointments were routine follow-ups, thus these subjects (N=45) provided a range of disabilities, disease durations, and types of MS, allowing the overall validation sample to span a broad spectrum of disease characteristics, and permitting some generalisability from the results. When comparing the demographic and clinical characteristics of the patients recruited from the inpatient Neuro-Rehabilitation Unit (NRU), who completed the longer battery of neuropsychological tasks, with those who undertook the short battery of cognitive tests, the groups differed with respect to: whether they had children, educational level (although NART-R IQ did not differ), type of MS (SP MS was predominant in NRU patients), and level of disability (NRU patients were more disabled). These differences were considered unremarkable, given the admission policy of the NRU, which specifies that patients

with severe and complex disabilities requiring multidisciplinary intervention are selected (Johnson & Thompson, 1996).

Despite the clinical characteristics of the patient group spanning a range of disease durations, disease types, and disabilities, and the comparable age of disease onset, to that reported in natural history studies, the level of disability assessed using the EDSS was higher in the current patient group than that reported in studies of community based MS patients. Rao et al. (1991a) recorded a mean EDSS of 4.1 in a study of cognitive function in community based patients (N=100), whist in the current study the mean EDSS was 6.2. Although the range of disability exhibited by the current patient group was large (1.5 - 9.0), individuals with minimal disability (i.e. EDSS scores of 0.5 & 1.0) were not represented. This finding suggests that the bias inherent in many projects conducted at established research centres and teaching hospitals is very difficult to eliminate, and that the results of the current study may not be generalisable to patients with mild disability. Similarly, in the interpretation of the 95% confidence intervals, reported to be small for the conventional neuropsychological tasks and the New Test Of Memory, as the sample is not random, and has some bias towards the recruitment of more disabled patients, it may not be truly representative of the MS population, and there may be some limitations in the generalisability of findings. A further implication of the patient group covering a slightly smaller range of EDSS scores, neglecting to represent individuals with very mild disability, is that the correlations of performance on the New Test Of Memory with disability may be weaker than those reported using a patient sample which comprises individuals exhibiting the entire range of levels of disability. As the disability spectrum is reduced, the possibility of a significant, strong correlation is also diminished. It must be noted, however, that, to date, the literature in this area is unclear, with mixed findings recorded. Patients with minimal disability are

infrequent in a specialist hospital as they have few complex problems requiring consultation with a neurologist. Furthermore, the New Test Of Memory was developed to provide a comprehensive memory assessment, applicable to patients with coexisting cognitive and physical deficits, hence the greater prevalence of moderately to severely disabled patients was not considered to be a major limiting factor.

2.9.2.2 Neuropsychological Features: Conventional Tasks

The patients who completed the short and long neuropsychological test batteries did not differ in terms of their premorbid IQ (estimated using the NART-R), or their performance on the measures of general verbal skills (WAIS-R vocabulary subtest), or spatial reasoning ability (VESPAR). The NART-R provides an estimate of optimum intellectual function, and the finding that the two groups did not differ on this variable suggested that the premorbid intelligence of the patients comprising the two groups was comparable. The vocabulary subtest of the WAIS-R and the spatial analogy section of the VESPAR assess current or actual levels of ability in the verbal and spatial domain, respectively. The lack of significant differences between the two groups on these variables suggested that the current intellectual abilities of the two groups were also analogous. The absence of significant differences between the two groups on these fundamental neuropsychological measures, and the unsurprising differences between their demographic and clinical features, were considered to indicate sufficient similarity between the profiles of the patients to allow the data from the short battery and long battery groups to be taken together for the purposes of comparison with the healthy controls. The lack of significant differences between the neuropsychological characteristics of the short battery and long battery patients, cited above, do not

guarantee equality of cognitive ability (e.g. as fatigue may affect cognitive performance, it could be speculated that patients who completed the long battery were more fatigued due to their rehabilitation programme; conversely, it could be argued that the short battery patients, who were recruited following a clinic appointment, were more fatigued due to travelling time, waiting time, and the previous neurological consultation). However, having considered possible objections to the amalgamation of data where appropriate, it was decided that the equivalence of the three main cognitive variables between the two groups constituted sufficient justification.

The confidence limits around the mean NART-R, VESPAR, and WAIS-R verbal IQ scores of the validation sample (Tables 2.8.3 to 2.8.5) were small, suggesting that accuracy had been achieved. The 95% confidence interval has a probability of 0.95 of containing the population value (Armitage & Berry, 1994), and, if the limits are close to the mean value reported, they indicate that the patient sample provides a reliable estimate of the MS population, and that there may be generalisability from the results.

As expected, the MS patients who completed the long battery of neuropsychological tasks demonstrated memory deficits on conventional assessments (Tables 2.8.5 & 2.8.6). However, these memory tests are thought to penalise automatically patients with coincident physical and/or cognitive handicaps (Section 1.4), causing them to have been criticised extensively (Section 1.9). These shortfalls were illustrated in the current study, where five patients were unable to complete one or more of the subtests of the WMS-R due to poor visual acuity and/or severely compromised manual dexterity (Section 2.7.2). Using the cognitive impairment criteria of "at or below two SDs of the published age group control mean", the memory deficiencies of the MS patients appeared to be more prevalent in the verbal, rather than the visuo-spatial, domain (Table 2.8.6). However, in addition to the issues concerning

the appropriateness of the tests for patients with MS, these impairment cut-offs (detailed in Section 2.8.2) were calculated using the published norms available in the test manuals. The use of published standardisation samples may lead to inaccuracies, because the data are not contemporaneous. These data were collected in the mid 1980s, from varying countries, using different sized control groups, which reduces precision for the evaluation of current data. Despite these concerns, the tasks used are well known in both the neuropsychological literature and the clinical community, and the data from these tests allow comparisons with other studies. Contemporaneous control data on the conventional memory tasks were not collected in this study due to practical constraints on the duration of the testing session. Approximately 80% of the healthy volunteers were in full-time employment. To prevent disruption of the working day, for those who had volunteered through their employing organisation, and, for others, to allow the tasks to be fitted into a lunch hour or after-work session, it was necessary for the battery of tests to be brief.

2.9.2.3 Neuropsychological Features: The New Test Of Memory - Performance

The subjects comprising the validation sample exhibited a range of scores on the New Test Of Memory, for both verbal and spatial recall memory, paired association, and recognition memory, at the Task Familiarisation stage, and at the two levels of difficulty (Tables 2.8.7 to 2.8.9). These findings, together with the cumulative frequency graphs (Figures 2.8.1 to 2.8.15), illustrate the capacity of the new measure to grade ability, and suggest that the test has the potential to be sensitive to change.

As previously mentioned, the confidence limits around the patient composite scores on the New Test Of Memory (Table 2.8.8 & 2.8.9) were small, again suggesting

accuracy. The tight boundaries around the mean indicate that the patient sample is providing a true representation of the MS population, and hence permits generalisability from the results.

Unlike the controls, patient performance on the New Test Of Memory did not correlate with age and sex. Composite verbal and spatial totals, and the overall total on the new measure only gave significant correlations with estimated premorbid IQ (Table 2.8.10). The effects of age and sex may have been eradicated due to the size and variation of the deficits in the MS group.

Performance on the verbal and spatial Task Familiarisation stage of the New Test Of Memory correlated significantly with equivalent IQ on the spatial analogy section of the VESPAR (Tables 2.8.11 & 2.8.12). This suggests that in the patient group, intelligence does significantly affect ability to learn the actual tasks of the new measure. Perhaps individuals with higher intelligence are more aware of their poor ability to grasp task demands, and/or patients with deteriorating intelligence are less able to learn the tasks. The correlations of performance on the Task Familiarisation phase with that of Sets 1 and 2 (Table 2.8.14) illustrate that there is a significant relationship between training and declarative memory performance, and this provides support for the inclusion of the scores at the Task Familiarisation stage in the composite totals on the New Test Of Memory. The finding also demonstrates that, in the patient group, learning the actual tasks is a constituent of overall memory performance.

The comparison of patient performance on the New Test Of Memory with that of the controls, also illustrated by the cumulative frequency graphs (Figures 2.8.1 to 2.8.15), showed the poorer memory abilities of the MS patients, across all domains and both difficulty levels. The mean composite scores of the patient group for verbal and spatial recall memory, paired association, and recognition memory, were significantly

below those of the control sample, with the exception of performance on the spatial paired association and spatial recognition memory tasks, where the trend did not reach statistical significance. This was due to the greater variation of ability on the spatial, as opposed to the verbal sections, in the healthy controls. In addition, the difficulty of the verbal and spatial stimuli may not have been precisely equivalent, as the verbal items are real words, hence semantic cues may be employed, whilst the spatial stimuli are nonsense shapes. This content artefact is discussed further in Section 3.1.3.

The mean scores of the patients at the Task Familiarisation stage and the two difficulty levels, for both the verbal and spatial modalities, were also significantly lower than those of the controls, and demonstrated the patients' impaired ability to learn tasks, and their deficient overall memory capabilities.

As expected, the range of patient scores tended to start below that of the controls, with a greater number of patients scoring at the lower end of the scale for a given memory domain or difficulty level (Figures 2.8.1 to 2.8.15). The coherence of the verbal and spatial difficulty levels of the New Test Of Memory was confirmed by Figures 2.8.16 to 2.8.21, where, as expected, patients who scored poorly on a given level, obtained a low score overall. Likewise, there was an increase in the number of patients classed as impaired with the increment in difficulty from Set 1 to 2 (Table 2.8.23).

A relatively small number of patients declined to complete the final verbal and/or spatial set(s), and as these subjects did not differ demographically, clinically, or cognitively (including performance on the Task Familiarisation stage and Set 1, the easier level of the new measure) from those who undertook Set 2, multiple regression was used to predict their scores, on the sections they declined to complete. One of the problems of using a multiple regression equation, and substituting the values for

missing data, is that the standard deviation of the predicted values will be smaller than the standard deviation of the data collected. However, the number of substitutions was limited, and the procedure was adopted in the later stages of the analyses, therefore the psychometric properties of the new measure were evaluated before the insertion of the predicted scores, and were thus free of any additional error variance.

2.9.2.4 Neuropsychological Features: The New Test Of Memory - Pattern Of Impairment

The poor performance of the patients on all the memory domains of the New Test Of Memory, was illustrated by the percentage of patients scoring at or below the 5th, 25th, and 50th percentiles of the controls (Table 2.8.21). Using the memory impairment cut-off of "at or below two SDs of the age group control mean" (Table 2.8.21), the trend for verbal memory to be more frequently impaired than spatial memory, noted with reference to Table 2.8.6, was maintained. Despite this, the incidence of dysfunction for both verbal and spatial recall memory and paired association, was slightly lower than that reported using the conventional tasks (Table 2.8.6), whilst for verbal and spatial recognition memory, there were a greater number of subjects classed as impaired using the new test. It is possible that the use of contemporaneous controls may have been partly responsible for these differences. Error variance is reduced by comparing patient performance with that of healthy individuals from the same geographical region, who have an identical demographic profile, and are tested over the same time period, as the patients. In addition, the saliency of the stimuli can be equated across both the patient and control groups, again minimising a possible source of variance. The purer measure of memory, which did not automatically penalise

patients with coincident physical and/or cognitive handicaps, may also have made a partial contribution.

Further analyses of the pattern of memory dysfunction demonstrated by the patients revealed that subjects were inclined to be categorised as impaired on more than one memory domain, within the verbal or spatial modality (Figure 2.8.22). This suggests that verbal or spatial memory deficits do not fractionate extensively in MS, and an impairment may impact on the efficiency of the various memory processes within the verbal or spatial domain. Table 2.8.22 provides further support for deficiencies in the general memory processes, where a number of patients exhibited dysfunction in both the verbal and spatial domain for a given type of memory (e.g. recall, paired association or recognition). These findings are consistent with the earlier results on the new measure, which suggested deficits in the necessary initial cognitive processes involved in both verbal and spatial memory, and/or disruption of the distributed networks used to encode, store, and retrieve information. Using an impairment index, based on the number of SDs below the age group control mean to which a patient's score fell, the range in severity of the various memory deficits was also demonstrated (Table 2.8.24). The heterogeneity of cognitive dysfunction in MS was illustrated by the variation in the severity of the memory impairment, relative to the range in IQ deterioration (Table 2.8.25). These findings also demonstrate that although performance on the New Test Of Memory correlates with intelligence, the test is not solely driven by IQ.

2.9.2.5 Neuropsychological Features: The New Test Of Memory - Relation To Clinical Measures

Patients categorised as impaired, using the cut-off of "at or below two SDs of the age group control mean", did not exhibit demographic or clinical characteristics significantly different to those patients classed as intact. These findings support previous research, and confirm the results reported in Table 2.8.18, which show that there were no significant correlations between performance on the New Test Of Memory and disease duration, or level of disability. The absence of a significant relationship between level of depression and performance on the new measure suggests that the patients' poor cognitive performance was unlikely to be due to affective factors. Performance on the New Test Of Memory correlated significantly, in a negative direction, with both the overall Function Systems score, and with the cerebral section of this measure (Table 2.8.18). As performance on the new measure did not correlate with scores on the visual or pyramidal systems, and in accordance with previous work, the current study demonstrated no significant relationship between cognitive performance and physical disability. They also indicate that the New Test Of Memory is appropriate for the assessment of memory in patients with visual disturbance and motor dysfunction, and suggest that the new test is sensitive to the detailed assessment of neurological impairment.

The significant negative correlation between the cerebellar section of the Functional Systems and the composite score on the verbal sections of the New Test Of Memory (Table 2.8.18), may have been an artefact of the number of statistical correlations conducted. It seems improbable that cerebellar disturbance, which is often manifest as ataxia, would influence performance on the verbal sections of the new measure, where sensori-motor demands are minimal. An alternative explanation is that

it represents cerebellar dysarthria. However, as only the verbal recall sections necessitate speaking (the paired association and recognition sections provide an alternative response mode), this seems unlikely. Scores on the brain stem section of the Functional Systems gave significant negative correlations with both verbal and spatial composite totals, and the overall total score on the New Test Of Memory. Brain stem dysfunction typically leads to nystagmus, dysarthria, and problems with speech and swallowing. However, as the new assessment utilised stimuli which were widely spaced on the page, and comprised tasks which required minimal speech output (verbal recall being the only section where speech is essential), it seems unlikely that such factors would impact significantly on cognitive test performance. An alternative explanation may be that scores on this section of the Functional Systems reflect damage to the thalamus, a structure which has been shown to be involved in higher cortical functions, namely, episodic memory. Schott et al. (1980), Winocur et al. (1984), and Von Cramon et al. (1985), all reported that focal lesions in the thalamic nuclei may be a possible cause of amnesia. More recently, Fazio et al. (1992) and Perani et al. (1993), using positron emission tomography (PET), demonstrated a significant bilateral reduction of metabolism in a number of interconnected cerebral regions including the thalamus, in patients with pure global amnesia, relative to healthy controls. Furthermore, Paulesu et al. (1996) recorded regional hypometabolism in the thalamus of patients with MS who were classed as memory impaired, when compared with both healthy controls, and MS patients without memory deficits. They commented that the limited spatial resolution of PET prevented the identification of individual thalamic nuclei, prohibiting the outright exclusion of the hypothesis that the observed thalamic hypometabolism resulted from disruption of the somatosensory pathways connected with specific thalamic nuclei, which are not involved in memory. However, Paulesu et al. (1996) noted that patients

with memory deficits did not differ in terms of physical disability from the memory intact MS patients who did not show hypometabolism of the thalamus, nor did the two patient groups show any significant differences in the regional cerebral glucose metabolism in the primary somatosensory or motor cortex. Paulesu et al. (1996) therefore suggested that the observed thalamic hypometabolism may have been due to demyelination of the extensive neuronal connections between specific thalamic nuclei and cortical regions involved in memory function.

There are a number of organically distinct memory systems, which historically were identified by lesion studies, and more recently, have been confirmed by functional imaging research. These studies have demonstrated the involvement of the left temporal-parietal cortex in phonological short term memory, whilst both parietal cortices, although predominantly the right, and the dorso-lateral and ventral prefrontal cortices have been implicated in visuo-spatial short term memory processes (Frackowiak et al., 1997). Studies of episodic memory have demonstrated the involvement of both subcortical (thalami, cerebellum) and cortical (medial temporal lobes, prefrontal cortices, posterior cingulate cortices, precuneus) regions. More specifically, it appears that encoding is most reliant on the left prefrontal cortex and the retrosplenial cortex, whilst the right prefrontal cortex and the precuneus are implicated in retrieval processes (Shallice et al., 1994).

The New Test Of Memory assesses memory processes which exceed the limits of phonological and visuo-spatial short term memory, and although some elements of these processes may be involved, the focus of the new measure is the evaluation of long term memory. The impaired performance of the MS patients relative to the control group, on both the verbal and visuo-spatial recall memory, paired association, and recognition memory sections may suggest that certain anatomical regions have been

damaged by the disease process (i.e. the prefrontal cortices, the posterior cingulate cortex, the precuneus). However, given the diffuse pathology of MS, and the variety in severity and pattern of the memory deficits exhibited by the patients, attempting to identify specific regions responsible for memory dysfunction in groups of MS patients may be of limited value. Demyelination and axonal loss have been reported in cortical and subcortical regions in MS, and these may impact on the brain regions, or on the nerve fibres linking these areas, the integrity of both being necessary for efficient verbal and visuo-spatial memory. In the current study, memory did not fractionate extensively in the patient group, implying deficits in the processes involved in both verbal and visuo-spatial memory, that is, not specific to a given modality. Patients also tended to be impaired in more than one memory domain, suggesting that the memory dysfunction was not localised to a specific memory process (i.e. recall, paired association, recognition). It is probable that MS disrupts the functioning of the distributed networks of memory at many points. These networks inevitably involve the co-ordination of a number of regions which are anatomically distinct, and may be connected by myelinated nerve tracts. Thus, plaques or many small areas of demyelination that coincide with a memory network may have a disproportionately large effect on the efficiency of memory processing, when compared with a similar amount of pathology in a localised anatomical region. Demyelination reduces the conduction ability of the nerve fibres resulting in slow and inaccurate transmission of the impulse carrying the information from one region of the memory network to another. Whilst individual patients may demonstrate functional dissociations of memory, the disseminated pathology of MS means that these are seldom captured by group studies.

Performance on the composite verbal and spatial totals of the New Test Of Memory and the overall total score correlated strongly with the cognitive section of the FIM (Table 2.8.18). The FIM is an assessment tool which evaluates patients' ability to carry out everyday functions, and the cognitive sections assess comprehension, expression, social interaction, problem solving, and memory (Section 2.7.1). Four of these items correlated significantly with memory performance; unsurprisingly, social interaction was not significantly related to performance on the New Test Of Memory. These results suggest that the new test, despite being abstract, assesses memory relevant to functioning in the real world. It also implied that there is a link of test scores with behavioural observations of competency in basic daily tasks.

2.10 THE PATIENT SAMPLE: CONCLUSIONS

Thus, examination of the validation sample data would suggest that the New Test Of Memory has fulfilled the criteria originally outlined. The design of the new measure appeared appropriate for the MS patients, being applicable to subjects with limited manual dexterity, poor visual acuity, speech difficulties, and/or coincident cognitive deficits. Analyses of the patient scores demonstrated that the new test assesses verbal and spatial recall memory, paired association, and recognition memory at two levels of difficulty. The new assessment appeared sensitive in each of the memory domains, grading the range of memory abilities exhibited by the patient group. It also demonstrated good internal reliability, consistency, and validity.

Using the new measure and comparing patient performance with that of the controls, the patient group demonstrated memory deficits in both verbal and spatial recall memory, paired association, and recognition memory. Patients were inclined to exhibit impairment in more than one memory domain, which suggested that their deficiencies may be due to disruption of the initial, supplementary cognitive processes essential for memory, and/or non-specific memory processes

CHAPTER THREE: GENERAL DISCUSSION

3.1 EVALUATION OF METHODOLOGY

Specific criteria must be considered, when introducing a new neuropsychological measure, in order to demonstrate the psychometric properties and applicability of the new assessment tool (Mapou, 1988). Initially, in this study, a comprehensive literature review was undertaken, to provide intricate knowledge of research into memory function in MS (Sections 1.5 to 1.7). The types of tests previous studies had employed were identified, and the stimuli, task demands, and psychometric properties of the assessment tools carefully evaluated (Sections 1.9 & 1.10). In addition, detailed discussions with expert clinicians provided a definite idea of the relevant attributes lacking in current measures of memory. A sensitive memory test, comprising matched verbal and spatial assessments, which placed minimal demands on sensori-motor functions and functionally separable cognitive skills, and spanned a range of capabilities, was desired (Section 1.11). Extensive piloting of stimulus items and task formats was then conducted to ensure that an appropriate test structure was created (Section 2.1). The new measure was therefore conceived and designed as a specific test of memory; a sensitive measure, which spanned the target ability spectrum, and made minimal demands on sensori-motor skills and other cognitive functions (Section 2.2).

3.1.1 The Samples:

Data from 85 control subjects were collected on a neuropsychological battery, which included the New Test Of Memory. The control sample comprised individuals with a broad range of ages and IQs, for both sexes. In the age group 18-40 years, a significant female preponderance was reported (previously discussed in Section 2.5). This may have exerted a mild influence on the mean scores recorded for the various sections of the New Test Of Memory. However, the patient group also demonstrated a higher incidence of female than male subjects (Section 2.8.1), and, as the patient data did not demonstrate any sex effects on the new measure (Section 2.8.3), the impact on the comparisons of patient and control scores would have been minimal. The validation sample comprised 100 MS patients with a range of demographic, clinical, and cognitive characteristic, which were considered representative of the MS population (Section 2.8.1). The 95% confidence intervals around the mean scores of the patient and control data, on both conventional neuropsychological tasks, and the New Test Of Memory were narrow (Sections 2.4.2, 2.4.4, 2.8.2 & 2.8.3). This suggested that the samples represented their respective target populations, and that the findings of the current study were likely to be reliable and replicable, indicating the potential for generalisability from the results.

As noted in Section 1.11, the target population for the standardisation sample consisted of healthy individuals of both sexes, with a variety of ages and levels of intelligence, retired from, or in, full-time employment. The target patient population were individuals with clinically definite MS, who required ongoing attention from a consultant neurologist (i.e. MS patients attending hospital). Despite attempts to ensure that both samples were representative of their respective target populations, the

possibility of a selection or sampling bias (Anastasi, 1976; Schwartz & Fox, 1995) in the composition of both the control and patient groups of the current study must be considered. This is a common problem in research studies (Anastasi, 1976; Schwartz & Fox, 1995). Individuals who volunteer may not be strictly typical of the specified population, or the sample may not encompass the diversity of characteristics found in the entire target population.

Controls often agree to participate in a research study because they have some professional or personal affiliation with the topic, hence they may not constitute an unbiased representation of the healthy population. There are many potential sources of bias when recruiting controls. Healthy volunteers, who know they are acting as control subjects providing data, which will be used to create a baseline of intact functioning, may be more relaxed and confident in their cognitive abilities. They may therefore perform to the best of their ability, that is, at their optimum level. Conversely, a control who has in-depth knowledge of the cognitive deficits characteristic of the disease, may falsely under achieve in an attempt to minimise any discrepancies between the cognitive performance of the patients relative to that of the controls. Healthy individuals may also volunteer because they fear they may have neuropsychological difficulties or may have experienced a deterioration in their cognitive skills, and therefore seek clarification through testing. Approximately 80% of the controls assessed in the current study were in full-time employment, 7% were housewives, and 13% were retired. There were no individuals in the control sample who were actively seeking work, therefore, it must be noted that the standardisation sample, although representative of the target population, may not include the demographic profile of those individuals who are unemployed.

Different factors may influence patient recruitment. Patients often volunteer because; they have been approached by their physician, they are motivated to participate

in a research project relevant to their condition, and they have the time readily available (Schwartz & Fox, 1995). These factors are unlikely to render the study unrepresentative of the relevant target patient population. However, it must be noted, that all participants of the current study were reasonably comfortable completing neuropsychological tasks, and did not suffer from significant test anxiety. Therefore, the study may not be representative of individuals who are adverse to cognitive assessment. Although there is the possibility that individuals, distressed by neuropsychological tasks, would always decline to complete an assessment, patients undergoing extensive medical investigations may be prepared to endure the evaluation. Test anxiety tends to evince under achievement (Mandler & Sarason, 1952), hence, an anxious patient, who is aware of the potential cognitive decline associated with their condition, may under perform during a neuropsychological assessment. All subjects comprising the patient group were recruited from a specialist hospital, and were under the care of three consultant neurologists. They therefore represented the target patient population. However, although the clinical characteristics of the patients did not appear to differ from those reported in natural history studies of MS patients using clinic-based or geographically-based patient groups (Section 2.9.2.1), the findings of the current study may not be generalisable to patients with MS who do not require or seek specialist contact. The characteristics of the patients who were excluded from the current study (Section 2.7.2) are, by definition, not represented by the target patient population. Therefore, the findings are not generalisable to patients with significant behavioural problems, which render assessment inappropriate.

The fact that patients with MS were less likely to be employed than the controls, which as noted previously reflected their chronic neurological disease, may have impacted marginally on the comparison of the neuropsychological features of patients

and controls. Rao et al. (1991b) reported that MS patients with cognitive impairment were less likely to be employed, therefore, ideally, a comparable proportion of the controls should have been unemployed. However, given the criteria of the target population, and the practicalities of recruitment, this discrepancy was considered unavoidable.

3.1.2 The New Test Of Memory:

Following detailed analyses, the control sample was considered to provide coherent normative data on the New Test Of Memory (Section 2.4). The new measure demonstrated high internal reliability and consistency (Cronbach's alpha, correlation matrices; Section 2.4.5), and construct validity was established by evaluating the relationship of the new test with tasks which assess similar functions, and by the results of the factor analyses (Section 2.4.6). Face validity was also shown (Section 2.4.6). The cumulative frequency graphs illustrated the sensitive grading of scores across the ability spectrum of the healthy control sample (Figures 2.4.4 to 2.4.18).

The format of the New Test Of Memory was demonstrated to be appropriate for the assessment of memory in the healthy population, and the restrictions necessary to allow applicability of the test for patients with coincident physical and/or cognitive handicaps did not render the assessment inappropriate for healthy volunteers. The New Test Of Memory demonstrated the age effects previously reported in the literature of memory function and healthy ageing (Section 2.4.4). As manual dexterity and visual acuity may decline with normal ageing, and the new measure relies less on these capacities than previous tests, this study provides additional support for these primary age effects. However, the data were based on a cross-sectional study, that is, the results

were derived from one assessment of several cohorts, involving a number of individuals of various ages. To provide further confirmation of the effects of ageing on memory performance using the new test, a longitudinal study would be required, that is, a follow-up which would examine any change over time.

Using the data from the validation sample, the new measure demonstrated strong internal reliability and consistency (Cronbach's alpha; correlation matrices; Section 2.8.4), and convergent, discriminant, and factorial, construct validity (Section 2.8.5). Face validity and discriminant validity were also shown (Section 2.8.5). The sensitivity of the test was established by the range of scores achieved by the patients, and the grading of ability across the target section of the memory spectrum, that is, from the moderately impaired to the bright intact (Figures 2.8.1 to 2.8.15).

The applicability of the new measure to the assessment of memory in the patient group was illustrated by the fact that all individuals (except one who has been detailed in Section 2.7.2) were capable of attempting the specified task for each verbal and spatial memory domain, at the Task Familiarisation stage and that of Set 1. In addition, performance on the New Test Of Memory did not correlate with the degree of disability as assessed by the EDSS, with the time to complete the NHPT, a measure of manual dexterity, or with the visual systems section of the Functional Systems (Sections 2.8.5 & 2.8.10). These findings suggest that the tasks comprising the new measure are relatively independent of the physical requirements, which often confound conventional memory tasks.

3.1.2.1 Task Familiarisation And Two Levels Of Difficulty:

The New Test Of Memory comprised a Task Familiarisation stage, followed by two levels of difficulty (Section 2.2). The range of scores on Sets 1 and 2, for both patients and the controls (Sections 2.4.4 & 2.8.3), suggest that the measure spanned the target ability spectrum, that is, from the moderately impaired to the bright intact. The results also demonstrate the grading of scores, indicating sensitivity.

The most severely impaired portion of the memory spectrum was not addressed by the New Test Of Memory, as there is already a comprehensive set of assessments for grading memory capabilities at this level, which, due to the simplicity of the stimuli and task demands, are appropriate for the assessment of low level memory ability in the MS population (The Camden Memory Tests; Warrington, 1996; detailed in Section 1.11). In addition, as demonstrated by the current patient sample, individuals with MS demonstrate such profound or gross memory deficits comparatively rarely. Thus, as well as the added complexity of a measure which spans the entire ability spectrum, the assessment of individuals with marked deficiencies has already been adequately addressed. The Camden Memory Tests (Warrington, 1996) were not administered to subjects in the current study, because of the sector of the ability range which they evaluate. For the purposes of comparison, it was considered more appropriate to administer conventional memory tests of comparable difficulty to the new measure.

The format of the New Test Of Memory comprised verbal and spatial recall, paired association, and recognition memory tasks, at the Task Familiarisation stage, and that of two difficulty levels (Section 2.2). Possible priming and interference effects were minimised in the verbal sections by ensuring that an item only had the potential to appear on a single occasion throughout the entire test. Once a word had been randomly selected, it remained excluded from the item pool until all targets and distractors, for

every section of the test, had been chosen. Similarly, all spatial items were unique. In the spatial recall sections, the position of the bar was randomly assigned, and although the background shapes were repeated, sometimes within, and between Sets, the fill used for each recall section was different. In addition, subjects did not spontaneously report interference effects. For the spatial paired association and recognition sections, as well as the random generation of co-ordinates, the stimuli for the Task Familiarisation stage, Set 1, and Set 2, comprised a different number of points (Section 2.2.4); the spatial paired association and recognition items of the Task Familiarisation stage were constructed from four co-ordinates, those of Set 1, each comprised five points, and the stimuli of Set 2 each possessed six co-ordinates.

The advantages of employing a Task Familiarisation stage have been detailed in Section 2.2.1. In the current study, the practice effects notable in both control and patient performance from the initial, Task Familiarisation stage to that of Set 1 justify the inclusion of the preliminary phase (Sections 2.4.4 & 2.8.3). As both the verbal and spatial sections utilise a variety of tasks, and the spatial stimuli are unusual, the Task Familiarisation stage provides an opportunity for subjects to become accustomed to the format and requirements of the test. It also allows individuals to develop strategies.

In the control sample, performance on the Task Familiarisation stage did not correlate significantly with NART-R IQ (Section 2.4.4), suggesting that the Task Familiarisation phase utilises procedural memory, and that, in healthy individuals, high levels of intelligence are not advantageous in learning the tasks. Task Familiarisation allows procedural learning, that is, the learning of the actual task, or the skills required to complete the task. In the patient group, however, equivalent IQ on the spatial analogy section of the VESPAR did impact significantly on performance on the New Test Of Memory (Section 2.8.3). This suggests that in the patient group, the more intelligent

individuals are perhaps aware of their difficulties when attempting to grasp new tasks, hence the influence of intelligence on performance. Alternatively, patients with a deterioration in intelligence may be less able to learn the tasks.

The administration procedures for the New Test Of Memory were maintained from the Task Familiarisation stage through both Sets. In addition, subjects were not informed that the initial sections were included to allow familiarisation with the types of stimuli and tasks. These measures ensured maximum effort, and therefore optimum learning. Feedback of scores on the Task Familiarisation sections was not provided, because it was considered of limited value in a memory assessment. However, further information regarding the task procedures was given, if required. Performance on the Task Familiarisation phase of the New Test Of Memory correlated significantly with that of Sets 1 and 2, providing support for the suggestion that learning the actual tasks forms an integral part of overall memory performance. Given the features outlined above, scores on the Task Familiarisation stage were included in the composite totals.

3.1.2.2 Test Format And Content Artefacts:

The New Test Of Memory comprised recall memory, paired association, and recognition memory tasks, which were matched across the verbal and spatial modalities (Section 2.2). They therefore avoid systematic bias due to test format artefacts. However, the results of both controls and patients (Sections 2.4.4 & 2.8.3), which demonstrated superior performance on the verbal sections relative to the spatial recall, paired association, and recognition tasks, suggest that the spatial stimuli may be more difficult than the verbal items. Although the use of randomly selected words attempted to minimise any content artefacts, endeavouring to equate the saliency of verbal and

spatial items, it would appear that, as the verbal items are real words, which inherently possess semantic associations, they are more salient. In contrast, the spatial stimuli are abstract and novel. The spatial items were deliberately constructed such that instant verbal labels (i.e. object names) were not readily accessible, permitting the specific examination of spatial memory, with minimal use of verbal skills. However, these constraints appear to have increased the difficulty of the items.

3.1.2.3 Appropriateness And Relevance To Everyday Memory Function:

The New Test Of Memory is a relatively pure assessment of recall memory, paired association, and recognition memory for each of the verbal and spatial modalities, which endeavours to place less reliance on the physical and/or cognitive handicaps, which patients with MS may experience. All verbal and spatial items are presented visually (at a size appropriate for subjects with visual disturbances), and, together with a decision making process during the study phase of each section, these measures attempt to limit the impact of attentional dysfunction on the assessment of memory. The verbal sections of the new test use high frequency words and generous timing, which attempt to minimise the effects of language disorders. In addition, the verbal paired association and recognition test phases offer a choice of response formats (speaking or pointing), to facilitate responding. The spatial sections of the new measure employ visually simple shapes. The task demands of the spatial recall sections have been demonstrated to be appropriate even for subjects with severely compromised manual dexterity, whilst the paired association and recognition sections again employ two response formats to minimise task demands, and assist responding.

As previously detailed, the coincident physical and/or cognitive handicaps (Sections 1.2.1, 1.4.1 & 1.4.2) which patients with MS may experience, often render conventional neuropsychological tests inappropriate for the accurate measurement of memory (Section 1.9 & 1.10). For example, the logical memory section of the WMS-R (Wechsler, 1987), in which memory for two aurally presented stories is assessed, requires the skills of attention, comprehension, and language, to be functioning at a level of efficiency sufficient to permit the accurate measurement of verbal free recall memory. These supplementary cognitive and physical abilities may be compromised in patients with MS (Kujala et al., 1995; 1996b), hence subjects may be automatically penalised, confounding the assessment of memory function. Similarly, the Rey-Osterrieth figure (Rey, 1941; Osterrieth, 1944), in which the subject is required to draw a complex figure from memory, places emphasis on the planning component of cognitive processing, as well as good manual dexterity and visual acuity. It has been demonstrated that patients with frontal lobe dysfunction score very poorly on this task, which suggests that failure does not necessarily indicate impaired visuo-spatial memory (Spreen & Strauss, 1991; Lezak, 1995).

A possible shortfall of the New Test Of Memory may be that it lacks ecological validity. Ecological validity in this instance refers to memory relevant to the real world, rather than the 'laboratory setting' (Neisser, 1976). Although initial insights often come from the outside world, the laboratory environment tends to be the preferred research location, as it permits the development of theoretical studies conducted in intentionally controlled conditions. Many studies which adopt a naturalistic approach necessarily abandon experimental rigour, as the systematic control of variables is compromised.

The principles of ecological validity also apply to neuropsychological tests. Assessment tools like the Rivermead Behavioural Memory Test (Wilson et al., 1985;

1987b), a test battery comprising 12 brief tasks, (e.g. remembering a name, an appointment etc.), are relevant to everyday memory capabilities. However, they also require a number of other cognitive skills, creating a profile of 'ability to function' in the real world, but revealing little about an individual's specific memory capabilities. The trend for memory tests to possess ecological validity has drawn the emphasis away from purer, diagnostic measures, and led to a plethora of assessments which rely on a composite of cognitive skills, in order for everyday memory function to be assessed accurately. These tasks evaluate the memory skills used in everyday life, in the context of engineered, 'real-life' situations. However, such scenarios often rely on the interaction of numerous cognitive skills such as attention, language, visual perception etc., all of which need to be functioning efficiently for the accurate appraisal of the specific memory capability.

Despite the fact that ecological validity was not a priority in test design, the New Test Of Memory correlated strongly with the constituent items and composite cognitive score of the FIM (Section 2.8.5), a measure of everyday functioning in the real world. Although the cognitive section of the FIM is not particularly sensitive to high level cognitive deficits, demonstrating a ceiling level (Langdon & Thompson, 1999), the relationships reported suggest that the new assessment tool is sensitive to the cognitive skills required for daily tasks, and demonstrates that tests can be relevant to elementary, real world functions, without utilising those same, actual activities as part of the assessment scale. This is contrary to the findings of Reitman (1970), who identified the "decoupling problem". Reitman suggested that the 'laboratory setting' may be an ideal environment to maximise the opportunity of examining one system in isolation. In real life, however, there is interaction between different components, or functional systems,

involved in any functional task. He reported that the more successful the decoupling the less the data resembled everyday life.

The significant correlation of performance on the New Test Of Memory with the FIM (Section 2.8.5) also provides evidence of a link between behavioural observations of memory function and the objective test. This is consistent with previous findings which have demonstrated the increased accuracy of subjective reports of memory dysfunction, if the report is provided by a close observer of the patient, rather than the actual individual him/herself (McIntosh-Michaelis et al., 1991).

3.2 THEORETICAL CONSIDERATIONS / IMPLICATIONS OF FINDINGS

Previous research has detailed the occurrence of cognitive dysfunction early in the disease process of MS, and in the presence of limited physical disability (Heaton et al., 1985; Van den Burg et al., 1987). A number of studies have also reported no significant correlations between cognitive dysfunction and clinical variables (Marsh, 1980; Rao et al., 1984; 1985; Lyon-Caen et al., 1986; Beatty et al., 1988; Rao et al., 1989a; Jennekens-Schinkel et al., 1990a; Minden et al., 1990; Mariani et al., 1991; Maurelli et al., 1992; Patti et al., 1995). The findings of the current study using the New Test Of Memory are consistent with these reports, as performance on the new measure did not correlate with disease duration, or level of disability, as assessed by the EDSS (Section 2.8.5). Similarly, performance on the new assessment did not correlate significantly with level of depression, measured using the HADS (Section 2.8.5), again providing support for the results of several previous researchers (Surridge, 1969; Peyser et al., 1980; Lyon-Caen et al. 1986; Beatty et al., 1989; Rao et al., 1989b; Minden et al., 1990; Grafman et al., 1991; Rao et al., 1991; Schiffer & Caine, 1991; Krupp et al., 1994).

The patient sample performed more poorly than the controls, on the verbal and spatial recall memory, paired association, and recognition memory sections of the New Test Of Memory. However, the mean scores of the patients on the spatial paired association and recognition sections were not significantly lower than those of the controls, although there was a trend towards impairment. These results are broadly consistent with the majority of studies, which have examined memory function in patients with MS (Sections 1.5, 1.6, & 1.7). It must be noted that the previous studies

used a variety of sample sizes, patient groups, impairment cut-offs, and neuropsychological measures. They are discussed in detail below.

3.2.1 Recall Memory:

Patients performed more poorly than controls on the new assessment of immediate verbal free recall memory. Performance on the verbal free recall sections of the new measure can most accurately be compared with the findings of previous studies which administered list learning tasks, especially those where the component items of the list are not intentionally, semantically related to each other. The current findings support the majority of previous studies (Jambor, 1969; Beatty & Gange, 1977; Rao et al., 1984; Caine et al., 1986; Van den Burg et al., 1987; Litvan et al., 1988b; Beatty et al., 1988; 1989; Rao et al., 1989b; Minden et al., 1990; Pozzilli et al., 1991a; Rao et al., 1991; Maurelli et al., 1992; Swirsky-Sachetti et al., 1992b; Rao et al., 1993b; Filippi et al., 1994; Beatty et al., 1995b; Comi et al., 1995; Armstrong et al., 1996; Beatty et al., 1996; Kujala et al., 1996a; Rovaris et al., 1998; Camp et al., 1999). Only two of the studies which administered comparable tasks (Jennekens-Schinkel et al., 1990b; Amato et al., 1995) reported no significant dysfunction of immediate verbal free recall memory, relative to healthy controls. Jennekens-Schinkel et al. (1990b) used a task which required the subject to recall 10 nouns, taken from two categories (animals & occupations). They noted that if the items were presented visually (the closest approximation to the task in the New Test Of Memory), no impairment of immediate free recall memory was demonstrated. However, on using aural presentation, an immediate verbal free recall memory deficit was identified. The fact that the target list comprised only 10 items, taken from just two categories, may have facilitated recall,

and, as both presentation modes evinced an impairment of delayed free recall memory the discrepancy in the findings for immediate recall memory, may have been due to the increased task demands of the aural presentation format, where efficient attentional process would be a prerequisite. Thus the lack of significant free recall memory dysfunction in the study was probably due to a ceiling effect, that is, the task was not sufficiently challenging to identify any defects in ability. Amato et al. (1995) used the five items subtest of the Randt Memory Battery (Randt et al., 1980; Randt & Brown, 1986), where recall memory for five monosyllabic, high frequency nouns is assessed. This task has, by the nature of the small number of items, a limited range of scores, and it has also been reported to demonstrate a low ceiling level (Erickson & Howieson, 1986; Section 1.9.2.5 provides further details).

The method of analysis and chosen threshold determine the prevalence of dysfunction reported. The current study noted the percentage of patients impaired on a given memory domain using various cut-offs (Table 2.7.21), and, when compared with the impairment rates reported in the literature (Section 1.5.1.1), the incidence of verbal recall memory defects using the new measure approximates that recorded in other studies, which administered lists comprising unrelated items. The only exception is the study by Rovaris et al. (1998), who recorded 60% of patients as impaired. However, these researchers do not state their criteria for the definition of impairment.

Using the New Test Of Memory, patients with MS were significantly deficient on the assessment of spatial immediate recall memory. This supports the finding recorded by many researchers (Jambor, 1969; Staples & Lincoln, 1977; Grant et al., 1984; Rao et al., 1984; Caine et al., 1986; Beatty et al., 1988; Fischer, 1988; Franklin et al., 1988; Minden et al., 1990; Pozzilli et al., 1991a; Rao et al., 1991; Clark et al., 1992; Swirsky-Sachetti et al., 1992b; Rao et al., 1993b; Filippi et al., 1994; Beatty et al.,

1995b; Comi et al., 1995; Kujala et al., 1996a; Ryan et al., 1996; Rovaris et al., 1998; Camp et al., 1999), with only three studies reporting contrary results (Jennekens-Schinkel et al., 1990b; Maurelli et al., 1992; Ruchkin et al., 1994). Jennekens-Schinkel et al. (1990b) used the 7/24 Spatial Recall Test (Barbizet & Cany, 1968) to assess immediate visuo-spatial recall memory. This measure has a low ceiling level, and has been criticised because the display is easy to code as co-ordinates, and there is a large verbal component involved in the memory task (reviewed in Section 1.9.3.2). In addition, Jennekens-Schinkel et al. (1990b) compared patient and control performance using only one composite score of immediate recall, which may have masked significant results. The overall score was computed by summing the scores achieved over the five presentation-recall trials, one distractor trial, and the original pattern once again. These methodological issues may have contributed to their findings. Maurelli et al. (1992) used the visual reproduction subtest of the Wechsler Memory Scale (WMS; Wechsler 1945), while Ruchkin et al. (1994) administered the revised version of this task (WMS-R; Wechsler, 1987). Both these subtests are reviewed in Sections 1.9.1.1 and 1.9.1.2, and have been criticised for the verbal codeability of the target stimuli, and for the necessity of efficient sensori-motor functions. These factors may lead to spurious findings, with the verbal component of the stimuli facilitating performance, and patients, perhaps unable to complete the test due to the task demands, being selectively excluded.

The incidence of immediate spatial recall memory impairment noted using the New Test Of Memory was slightly lower than that recorded in previous studies. The percentage of patients classed as impaired will necessarily depend on the cut-off criteria adopted, hence the range in previously reported impairment rates (43% to 13%). However, the lower incidence currently recorded may be due in part to the increased

focus of the new assessment, where verbal coding is minimal, and the restricted impact on test performance of coincident physical, and/or cognitive, handicaps.

3.2.2 Recognition Memory:

In the current study, verbal immediate recognition memory, as assessed using the New Test Of Memory, was also recorded as deficient in the MS patients. As detailed in Section 3.2.1, the verbal recognition memory assessments of list learning tasks, with stimuli not deliberately semantically associated, are the most comparable to the new recognition measure. Previous research has reported mixed findings with regard to whether verbal recognition memory is deficient in patients with MS (Section 1.6.1). Several researchers have reported deficient verbal recognition memory using delayed assessments (Caine et al., 1986; Van den Burg et al., 1987; Beatty et al., 1988; Minden et al., 1990; Swirsky-Sacchetti et al., 1992b). Despite these findings, a number of studies recorded no significant difference between patients and controls on both immediate and delayed verbal recognition tests (Carroll et al., 1984; Beatty et al., 1989; Rao et al., 1989b; Jennekens-Schinkel et al., 1990b; Ron et al., 1991; Rao et al, 1993b; Armstrong et al., 1996). The three studies which noted no immediate verbal recognition impairment in their MS patient groups were: Jennekens-Schinkel et al. (1990b), Ron et al. (1991), and Armstrong et al. (1996). Jennekens-Schinkel et al. (1990b), employed the aural and visual presentation modes detailed in section 3.2.1, and reported that patients with MS did not perform at a level significantly different to that of the controls when the stimuli were presented visually, but when using aural presentation of the items, patients were impaired. This study has been discussed in Section 3.2.1. Ron et al. (1991) also noted no significant deficit of immediate verbal recognition memory in their patient

sample, when compared with matched healthy controls. They used the Recognition Memory Test For Words (Warrington, 1984), and commented that their finding of intact recognition memory may have been due to a lack of sensitivity in the measure (the test is reviewed in Section 1.9.2.7). Armstrong et al. (1996) utilised the RAVLT (Section 1.9.2.2), and also demonstrated normal immediate verbal recognition memory in their MS patients. However, the recognition memory assessment, although not specifically delayed, did follow five presentation-recall trials, which may account for the discrepancy between this study and the results reported using the new measure, where a format of one presentation-test phase was employed.

There is little consensus regarding whether visuo-spatial recognition memory is significantly impaired, or remains intact, in patients with MS (Section 1.6.2). In the current study, patients tended to perform more poorly than the controls, although, in the statistical analysis, the trend did not reach significance. 11.3% of patients scored at or below two SDs of the age group control mean, while 15.0% were classed as impaired if the fifth percentile was used as the cut-off. Only one previous study has reported intact immediate visuo-spatial recognition memory performance by MS patients (Carroll et al., 1984). Carroll et al. (1984) used pictures as the stimuli for their task, and these can easily be coded verbally, and may have facilitated performance on the assessment.

Many researchers have suggested that in MS, recognition memory, both verbal and visuo-spatial, is less affected than recall memory, although Rao et al. (1993b) has suggested that the discrepancy may be due to methodological issues. Rao et al. (1993b) noted that recognition tests are often easier than free recall tasks, and therefore group differences on recognition measures may be masked by a ceiling effect. The results using the New Test Of Memory do not provide unequivocal support for this notion, as the incidence of both immediate verbal and spatial recognition memory dysfunction in

the current study, was marginally higher than that of immediate verbal and spatial free recall memory, when a cut-off of at or below two SDs of the age group control mean was adopted. However, when various percentile cut-offs were examined, the incidence of immediate free recall memory deficits was higher for both modalities. These findings illustrate the influence of cut-off selection on the pattern and interpretation of results.

3.2.3 Paired Association:

Patient performance on the verbal paired association section of the New Test Of Memory was significantly below that of controls. The new measure used word pairings in which the items were not intentionally semantically associated, hence, previous studies which utilised stimuli of the same structure provided the most equivalent comparison. Much previous research has reported impaired performance on both immediate and delayed trials of verbal paired association tasks (Jambor, 1969; Staples & Lincoln, 1979; Rao et al.,1984; Huber et al., 1987; Fischer, 1988; Litvan et al., 1988b; Jennekens-Schinkel et al., 1990b; Minden et al., 1990; Clark et al., 1992; Maurelli et al., 1992; Amato et al., 1995; Comi et al., 1995; Kujala et al., 1996a; Ryan et al., 1996), and the studies which distinguish high from low associate word pairings all record significant dysfunction of immediate verbal paired association, in low associate pairs, in patients with MS (Fischer, 1988; Jennekens-Schinkel et al., 1990b; Minden et al., 1990; Maurelli et al., 1992). These findings are consistent with the current study.

Using the New Test Of Memory, patients performed poorly on the spatial paired association assessment, however, the overall mean score was not significantly different to that of controls. Only 2.5% of patients scored at or below two SDs of the age group control mean, while 12.5% scored at or below the fifth percentile. Three previous

studies noted significant impairment in visuo-spatial paired association (Beatty et al., 1988; Fischer, 1988; Beatty et al., 1989); with one study (Ruchkin et al., 1994) reporting intact performance by patients with MS. The tasks used by Beatty et al. (1988; 1989), Fischer (1988), and Ruchkin et al. (1994) have all been criticised for their strong verbal component, which renders them impure test of spatial paired association (Sections 1.9.2 & 1.10.2). The findings, therefore, remain unclear in this particular domain.

3.2.4 Summary:

Thus, patient results using the New Test Of Memory are broadly consistent with previous research. With respect to recall memory, the results of the validation sample provide support for the majority of earlier work, which assessed both the verbal and spatial domains. The current study reported a statistically significant deficit in patient verbal recognition memory, but only a trend for impaired spatial recognition memory. This would appear to reflect the inconsistent findings recorded in the literature. With regard to paired association; in the verbal domain, the current study supports previous work, whilst in the spatial modality, the paired association results remain inconclusive.

3.2.5 Deficit Theories:

There are various theories regarding the specific nature of the memory dysfunction exhibited by patients with MS (Section 1.8). The retrieval deficit hypothesis suggests that MS patients are able to encode and store information as efficiently as healthy subjects, but have difficulty when retrieval is required. Researchers cite impaired performance on free recall memory tests, but intact span memory, semantic

memory, recognition memory, and implicit memory of MS patients as evidence in support of this notion (Section 1.8.1). In contrast, DeLuca et al. (1994) reported that, if the amount of information initially encoded is controlled, the performance of patients on recall and recognition assessments is not significantly different from controls. They suggest that the memory impairments of MS patients are a consequence of inadequate initial learning or acquisition. Furthermore, they consider the deficient encoding to be due to the problems patients experience with the speed and efficiency of information processing (Section 1.8.2).

The results of the MS patients on the New Test Of Memory do not unequivocally support either the acquisition or retrieval deficit hypotheses. That patients were impaired on both the recall and recognition tasks in both modalities, when compared to controls, suggests deficiencies in more than one area of memory processing. If patients had been impaired on the recall tasks, but intact on the recognition assessments, retrieval deficits would have been the most probable explanation for their dysfunction. However, because patients recalled significantly fewer verbal and spatial items than controls, and performed more poorly on the verbal and spatial recognition sections, the pattern is suggestive of inefficiencies in any/all of the encoding, storage, and retrieval processes. This multiple deficit approach is supported by the findings, using the New Test Of Memory, that the patients tended to exhibit impairment on more than one memory domain within the verbal or spatial category, and were often deficient on the same type of memory task across both modalities (Section 2.8.7). This suggests that memory function in MS does not fractionate extensively, and that there are likely to be defects in the fundamental memory processing components.

Beatty et al. (1996) reported heterogeneity in the memory performance of their patients with MS (Section 1.8.3). Of 99 patients, only two subjects met the strict criteria

for pure retrieval failure. Beatty et al. (1996) suggested that the analysis of group means may not be the most appropriate method for examining the memory function of MS patients accurately, and, as few subjects exhibited a pure retrieval or encoding defect, any unitary disturbance of memory may be misleading. The current study supports these findings, suggesting that the memory deficiencies of patients with MS may not be explicable in terms of a single deficit hypothesis. It is probable that the patient group in this study, comprised subjects with a variety of different memory deficiencies, which cannot be accurately explained by either acquisition or retrieval deficit hypotheses alone.

3.2.6 Anatomical Considerations:

Using positron emission tomography (PET), it has been shown that the acquisition of episodic memories in healthy controls involves the left prefrontal cortex and retrosplenial area (Shallice et al., 1994). Fletcher et al. (1998a) found the left dorsolateral prefrontal cortex was specifically activated when executive processes were employed to create an organised structure, and this suggests the region is directly involved in the initial encoding of information. The retrosplenial cortex is an important pathway from this left prefrontal region to the hippocampus (Shallice et al., 1994), and Rudge and Warrington (1991), demonstrated that lesions of the retrosplenial cortex can result in an amnesic state, providing support for its involvement in memory function. Retrieval processes are associated with activation in the right prefrontal cortex and bilateral precuneus (Shallice et al., 1994). Fletcher et al. (1996) reported the precuneus to be involved in the imageability of stimuli, whilst their later study demonstrated that the right prefrontal cortex monitors and verifies the retrieval processes involved in

memory (Fletcher et al., 1998b). The dorsal region of the right prefrontal cortex is involved in controlling retrieval, whilst the ventral area shows increased activation when external cueing is employed (Fletcher et al, 1998b). Selective activation of the hippocampal system, a region known from lesion studies to be involved in memory, was lacking in these studies. This appears to be a consistent finding in PET studies of intact memory function (Squire et al., 1992; Grasby et al., 1993), and Shallice et al. (1994) suggested that this may be a result of the encoding processes in the hippocampus entailing sparse neuronal activation (Rolls & Treves, 1990).

Thus, efficient memory function in healthy controls appears to involve many different regions of the cerebral hemispheres. As MS results in multi-focal areas of axonal loss and demyelination, which may occur anywhere within the central nervous system, and which may interfere with the functioning of various different and interrelated systems, it is unremarkable that cognitive functioning, particularly memory, is often deficient in MS patients. Given the complexity of the memory system, and the unpredictable location of MS lesion, it is also unsurprising that the pattern of memory impairments demonstrated by these patients appears to be varied.

Despite the characteristically diverse location of lesions in MS, Swirsky-Sacchetti et al. (1992b) attempted to relate the position of cerebral white matter lesions to specific patterns of cognitive performance. With reference to memory, they found that lesions in the left frontal lobe predicted impaired encoding and recall of both verbal and visuo-spatial memory, lesions in the left parieto-occipital cortex predicted deficient verbal learning, and damage to the right parietal-occipital and right temporal regions predicted impaired recognition memory and visuo-spatial memory. However, Swirsky-Sacchetti et al. (1992b) did acknowledge that their study examined a relatively small

sample of patients (N=40), and used MRI, a technique which reveals little of the integrity of adjacent grey matter.

It has been reported that up to 26% of hemisphere lesions in MS patients are found outside the white matter (Brownell & Hughes , 1962), and Kidd et al. (1999) noted that MRI tends to under report the small cortical lesions often found in MS. In addition, Camp et al. (1999) recorded a significant correlation between cognitive impairment and a measure of cerebral volume, which included both grey and white matter, in patients with primary progressive and transitional progressive MS. These findings, therefore, suggest that grey matter lesions may contribute to cognitive dysfunction in patients with MS.

Paulesu et al. (1996) investigated the functional basis of memory impairment in MS using PET. They found that relative to healthy controls, MS patients with memory deficits showed bilateral reduction of regional cerebral glucose metabolism in the cingulate gyrus, thalamus, hippocampus, associative occipital cortex and cerebellum. When comparing patients with MS, who were classed as exhibiting memory deficits, with unimpaired MS patients, hypometabolism in the left thalamus and both hippocampi was reported. Paulesu et al. (1996) therefore suggested that the hypometabolism of thalamic and deep cortical grey matter structures of the temporal lobe is associated with episodic memory dysfunction in MS.

Thus it would appear that lesions in grey matter regions of the cerebral hemispheres may be implicated in memory dysfunction in MS. However, their contributions have been relatively unexplored, to date. Memory impairment may also be caused by demyelination of the extensive neuronal connections between specific thalamic nuclei and cortical areas. The studies detailing the location of lesions, and the research which indicates the variable profile of memory deficits, suggest that MS does

not fit comfortably within the confounds of the 'subcortical dementia' category. Recent work, including the current study, illustrate that explicit memory dysfunction in MS is unlikely to be due solely to retrieval deficits, and studies have documented the demyelination that may occur in cortical regions. These findings therefore suggest that MS does not qualify as a subcortical dementia.

3.2.7 Further Work:

Having completed the control series and the first validation sample of patients with MS, future work is under consideration. As the Task Familiarisation stage of the New Test Of Memory allowed subjects to learn the actual tasks of the measure, it would be of interest to create a parallel version of this set, and assess performance on a small number of items, following the Task Familiarisation phase. The test-retest reliability of the new measure should also be examined. In addition, although it has been demonstrated that the new test is as sensitive as conventional tasks, when administered in a cross-sectional study, it is important to ascertain if the test is able to discriminate accurately changes in ability over time. The development of parallel forms of the New Test Of Memory would be useful for longitudinal studies, and would allow the examination of the reliability and validity of the complementary versions, testing the hypothesis that the use of extensive randomisation removes the necessity for individual standardisation and validation of each form. Following such studies, the responsiveness of the New Test Of Memory to clinically relevant change could also be appraised.

On completion of these studies, the New Test Of Memory could be employed in natural history studies, and drug trials, which necessarily require serial assessment. The fact that the new measure takes account of physical and/or cognitive disability suggests

that it would be an appropriate assessment tool for a patient group, who may not be severely compromised at the start of a research project, but, who can exhibit pronounced physical and/or cognitive deterioration over the duration of the study.

As the New Test Of Memory has been demonstrated to place few demands on sensori-motor skills, and supplementary cognitive processes, it would be of interest to evaluate the appropriateness of the measure in other patient populations, where physical and/or cognitive disability may compromise test performance on conventional tasks.

Evaluating the role of the New Test Of Memory in guiding rehabilitation, and predicting its outcome, would also be valuable. In a stratified, wait-list controlled study of 66 MS patients in the progressive phase, Freeman et al. (1997) demonstrated that a period of inpatient multidisciplinary intervention significantly improved the patient's physical disability and handicap, although the level of impairment remained the same. Furthermore, Freeman et al. (1999) reported that, in a longitudinal study of 50 MS patients, again in the progressive phase, the benefits of rehabilitation were maintained for between six and nine months following discharge from the inpatient unit, despite declining neurological status. Therefore, in the context of unchanged neurology, the functional independence of patients with MS can be improved by rehabilitation, and, these benefits can be maintained over time, despite progressive deterioration in impairment. Although multidisciplinary intervention has been shown to benefit MS patients, Langdon and Thompson (1999) reported in a sample of 38 MS patients, that the patient's level of cognitive dysfunction impacted negatively on the outcome of their rehabilitation. Given the fact that the New Test Of Memory takes account of coincident physical and/or cognitive deficits, providing a more accurate measure of memory ability, the role of the New Test Of Memory as a guide to, and a predictor of, the outcome of the multidisciplinary intervention should be examined.

3.3 CONCLUSIONS:

Thus the new assessment provides a relatively pure memory measure, with minimal additional physical and cognitive task demands. The results from the standardisation and validation studies would suggest that the New Test Of Memory is a sensitive assessment of the variety of memory difficulties found in patients with MS. The matched set of memory tests have been developed to examine verbal and spatial recall memory, paired association, and recognition memory, and to be appropriate for the measurement of memory in patients with sensori-motor impairments and/or coincident cognitive deficits.

In conclusion, therefore, the New Test Of Memory provides a sensitive index of memory ability, relatively uncontaminated by coincident cognitive deficiencies and less restricted by compromised sensory and motor skills. It has been shown to be suitable for the graded assessment of both verbal and spatial explicit recall memory, paired association, and recognition memory, across a spectrum of capabilities, from the moderately impaired to the bright intact. In addition, the matched format of the tasks allows comparisons to be made between the modalities. Results using the new measure do not provide support for either the acquisition or retrieval deficit hypotheses alone. This would appear to suggest that the memory deficits of patients with MS do not fit a dichotomous model.

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APPENDICES

Appendix A: The Verbal And Spatial Stimuli Of The Task Familiarisation Stage Of The New Test Of Memory.

Appendix A1: The stimuli and task demands of the Task Familiarisation stage for the verbal and spatial recall sections (See pages 382-383 for a scaled version of the items used).

VERBAL RECALL:

Study Phase: Six words were presented individually, each for three seconds, during which time the subject was asked to decide whether the item was one he or she would use everyday.

Test Phase: The subject was asked to recall as many items as possible in any order.

SPATIAL RECALL:

Study Phase: Six shapes were presented individually. Each comprised a regular background shape, on which was positioned a bar. In each case, the subject was required to copy the position of the bar on the background shape, using the blank shape and a replica bar, both of which were provided. (An example of the stimuli, to size, is given on pages 408-409)

Test Phase: The subject was asked to position the bar on a given background shape from memory, again having been provided with the blank shape and a replica bar. Items were studied and tested in two groups of three, that is three items were studied and then tested, followed by a further study and test phase of the remaining three items.

Appendix A2: The stimuli and task demands of the Task Familiarisation stage for the verbal and spatial paired association sections (See pages 384-385 for a scaled version of the items used).

VERBAL PAIRED ASSOCIATION:

Study Phase: Three pairs of words were presented to the subject, each pair for three seconds. During this time the subject was asked to decide whether the items were words he or she would use everyday. (An example of the stimuli, to size, is given on pages 410-411)

Test Phase: The subject was presented with the first word of a pair and asked to select the second item, from six choices.

SPATIAL PAIRED ASSOCIATION:

Study Phase: The subject was presented with three pairs of shapes, each pair for four seconds, and asked to decide whether the items were shapes he or she could easily copy. (An example of the stimuli, to size, is given on pages 412-414)

Test Phase: The subject was given the first item of a pair and required to select the second item, from six choices.

Appendix A3: The stimuli and task demands of the Task Familiarisation stage for the verbal and spatial recognition sections (See page 386 for a scaled version of the items used).

VERBAL RECOGNITION:

Study Phase: Three pairs of words were presented to the subject, each pair for three seconds, during which the subject was asked to decide whether the items were words he or she would use everyday. (An example of the stimuli, to size, is given on page 415-416)

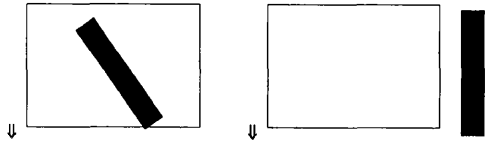
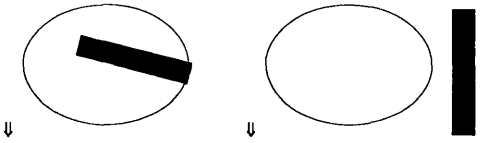
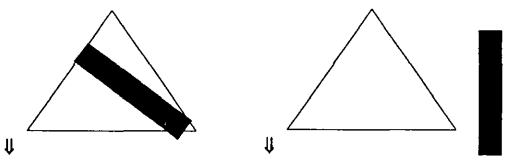
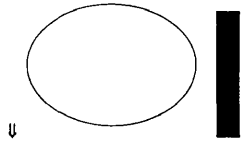
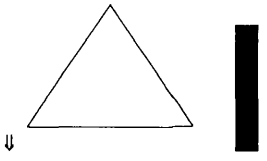
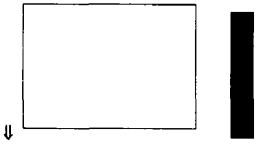
Test Phase: The subject was required to choose which of the two pairs of words had been studied previously.

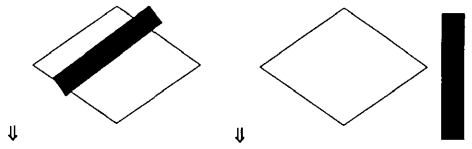
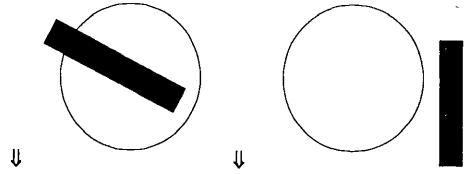
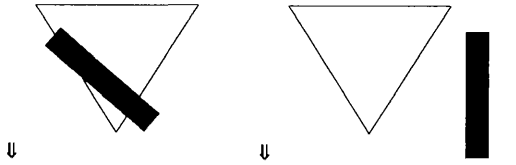
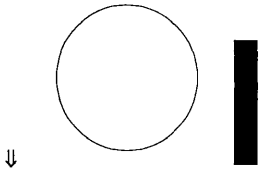
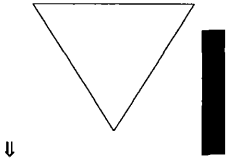
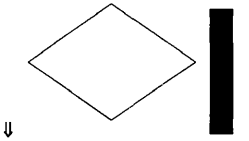
SPATIAL RECOGNITION:

Study Phase: The subject was presented with three pairs of shapes, each pair for four seconds, and asked to decide whether the items were shapes he or she could easily copy. (An example of the stimuli, to size, is given on pages 417-418)

Test Phase: The subject was required to choose which of the two pairs of shapes had been studied previously.

Appendix A1: The Stimuli (To Scale) Used In Verbal And Spatial Recall Sections, At The Task Familiarisation Stage (See Pages 408-409 For An Example Of The Fill Used For The Spatial Items, And The Items At Full Size).

VERBAL RECALL						
STUDY PHASE	1) **PEN**	2) **AIM**	3) **WHY**	4) **NATIONAL**	5) **MIND**	6) **STEP**
TEST PHASE	free recall					
SPATIAL RECALL						
STUDY PHASE	1) 		2) 		3) 	
TEST PHASE	1) 		2) 		3) 	

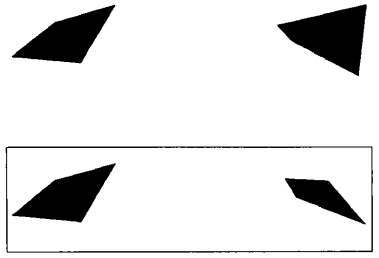
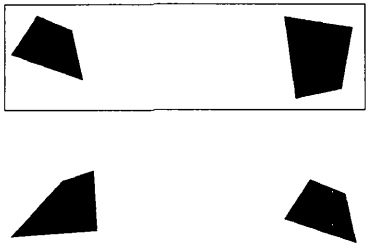
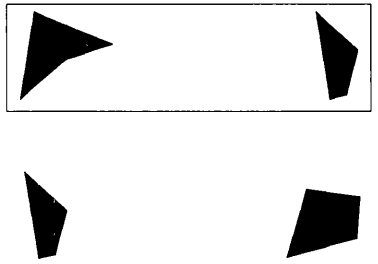
STUDY PHASE	4) 	5) 	6) 
TEST PHASE	4) 	5) 	6) 

Appendix A2: The Stimuli (To Scale) Used In Verbal And Spatial Paired Association Sections, At The Task Familiarisation Stage (See Pages 410-414 For An Example Of The Items At Full Size).

VERBAL PAIRED ASSOCIATION									
STUDY PHASE	1) **WHEAT - SURPRISE**			2) **PLENTY - SPEECH**			3) **FULLY - SHARE**		
TEST PHASE	1) **FULLY**	ROYAL BITTER SUMMER	MOTION **SHARE** SKY	2) **WHEAT**	**SURPRISE** BOTTOM SUN	WIT APPEAL MACHINE	3) **PLENTY**	EARLY REAL **SPEECH**	TURN OPPOSITE GENERALLY

SPATIAL PAIRED ASSOCIATION			
STUDY PHASE	1)	2)	3)
TEST PHASE	1)	2)	3)

Appendix A3: The Stimuli (To Scale) Used In Verbal And Spatial Recognition Sections, At The Task Familiarisation Stage (See Pages 415-418, For An Example Of The Items At Full Size).

VERBAL RECOGNITION			
STUDY PHASE	1) **DRAW - PIE**	2) **PURPOSE - TONIGHT**	3) **FLOOD - DANGEROUS**
TEST PHASE	1) **PURPOSE - TONIGHT** SPORT - TONIGHT	2) DESIGN - PIE **DRAW - PIE**	3) **FLOOD - DANGEROUS** FLOOD - TONGUE
SPATIAL RECOGNITION			
STUDY PHASE	1) 	2) 	3) 
TEST PHASE	1) 	2) 	3) 

Appendix B: The Verbal And Spatial Stimuli Of Set 1 Of The New Test Of Memory.

Appendix B1: The stimuli and task demands of Set 1 verbal and spatial recall sections (See pages 389-391 for a scaled version of the items used).

VERBAL RECALL:

Study Phase: Ten words were presented individually, each for three seconds, during which time the subject was asked to decide whether the item was one he or she would use everyday.

Test Phase: The subject was asked to recall as many items as possible in any order.

SPATIAL RECALL:

Study Phase: Ten shapes were presented individually. Each comprised a regular background shape, on which was positioned a bar. In each case, the subject was required to copy the position of the bar on the background shape, using the blank shape and a replica bar, both of which were provided. (An example of the stimuli, to size, is given on pages 419-420)

Test Phase: The subject was asked to position the bar on a given background shape from memory, again having been provided with the blank shape and a replica bar. Items were studied and tested in a group of three, then four, then three again, that is, three items were studied and then tested, followed by the study and test phase of four items, and then the remaining three items.

Appendix B2: The stimuli and task demands of Set 1 verbal and spatial paired association sections (See pages 392-393 for a scaled version of the items used).

VERBAL PAIRED ASSOCIATION:

Study Phase: Five pairs of words were presented to the subject, each pair for three seconds. During this time the subject was asked to decide whether the items were words he or she would use everyday.

Test Phase: The subject was presented with the first word of a pair and asked to select the second item, from six choices.

SPATIAL PAIRED ASSOCIATION:

Study Phase: The subject was presented with five pairs of shapes, each pair for four seconds, and asked to decide whether the items were shapes he or she could easily copy. (An example of the stimuli, to size, is given on pages 421-423)

Test Phase: The subject was given the first item of a pair and required to select the second item, from six choices.

Appendix B3: The stimuli and task demands of Set 1 verbal and spatial recognition sections (See pages 394-395 for a scaled version of the items used).

VERBAL RECOGNITION:

Study Phase: Five pairs of words were presented to the subject, each pair for three seconds, during which the subject was asked to decide whether the items were words he or she would use everyday.

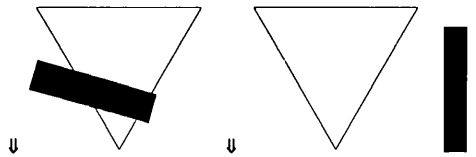
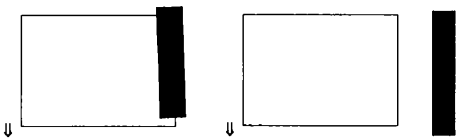
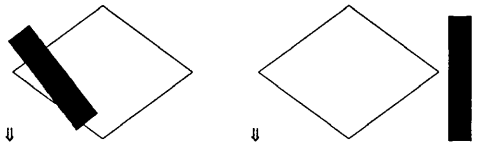
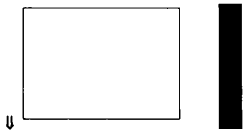
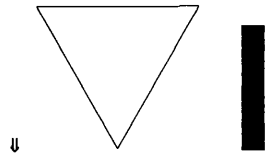
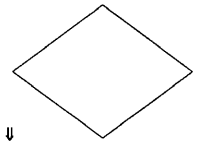
Test Phase: The subject was required to choose which of the two pairs of words had been studied previously.

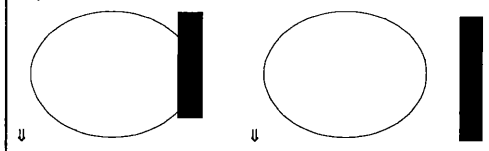
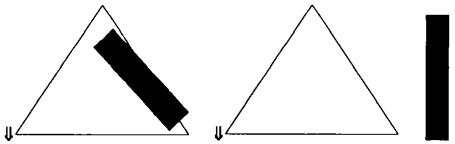
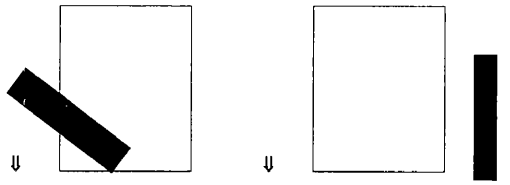
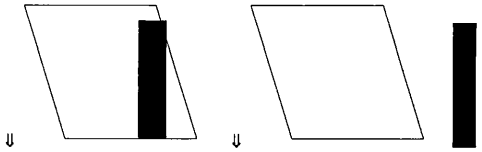
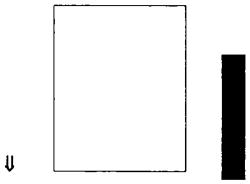
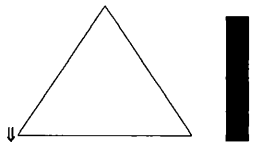
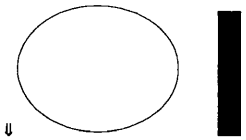
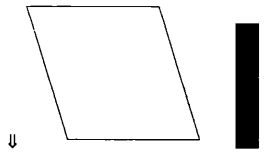
SPATIAL RECOGNITION:

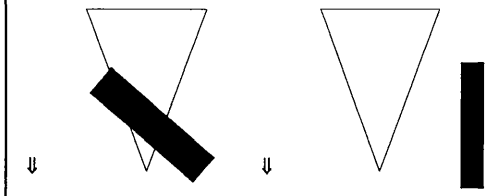
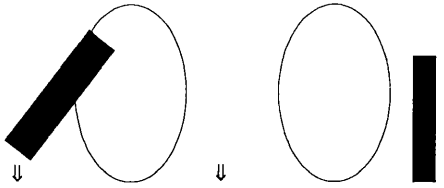
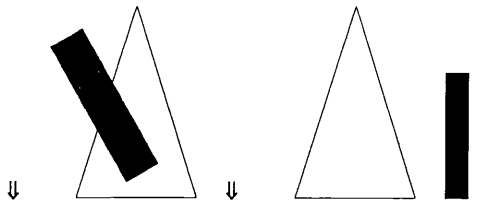
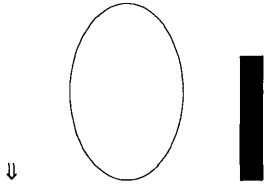
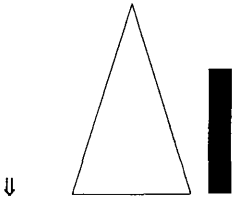
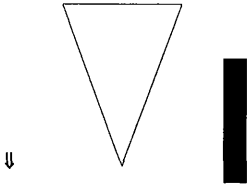
Study Phase: The subject was presented with five pairs of shapes, each pair for four seconds, and asked to decide whether the items were shapes he or she could easily copy. (An example of the stimuli, to size, is given on pages 424-425)

Test Phase: The subject was required to choose which of the two pairs of shapes had been studied previously.

Appendix B1: The Stimuli (To Scale) Used In Set 1 Verbal And Spatial Recall Sections (See Pages 419-420, For An Example Of The Fill Used For The Spatial Items, And The Items At Full Size).

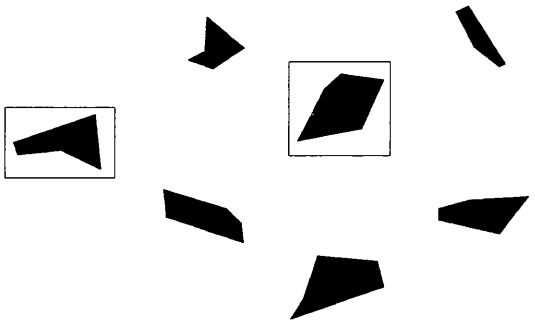
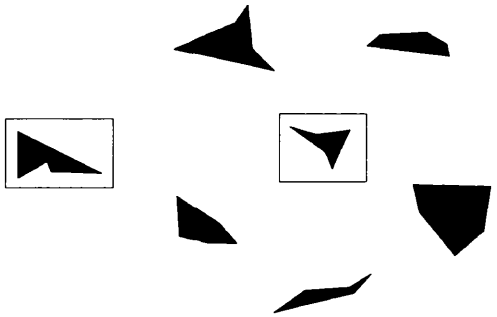
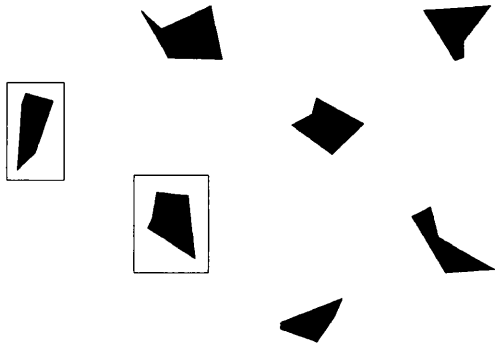
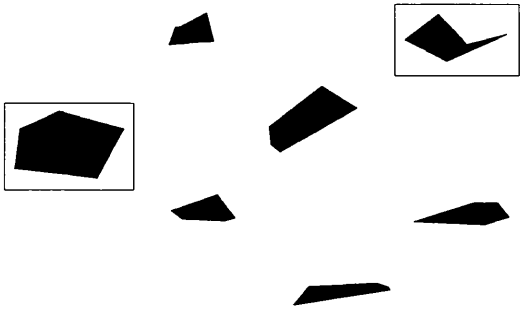
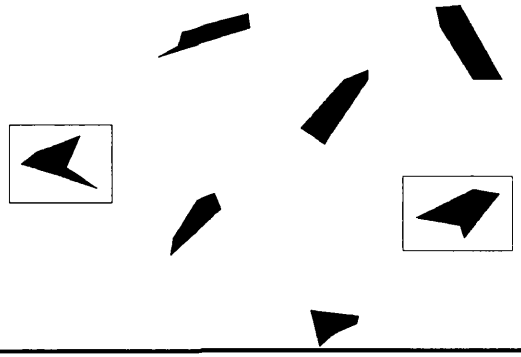
VERBAL RECALL						
STUDY PHASE	1) **INCREASE**	2) **DATE**	3) **DIFFERENT**	4) **FIGHT**	5) **HOWEVER**	6) **NUMBER**
STUDY PHASE	7) **PRESS**	8) **QUESTION**	9) **LOVELY**	10) **EXAMPLE**		
TEST PHASE	free recall					
SPATIAL RECALL						
STUDY PHASE	1) 		2) 		3) 	
TEST PHASE	1) 		2) 		3) 	

STUDY PHASE	4) 	5) 	6) 
STUDY PHASE CONT.	7) 		
TEST PHASE	4) 	5) 	6) 
			7) 

STUDY PHASE	8) 	9) 	10) 
TEST PHASE	8) 	9) 	10) 

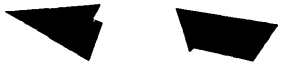
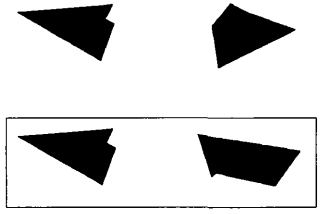
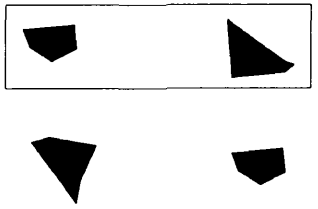
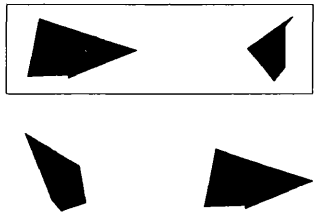
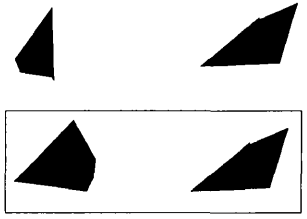
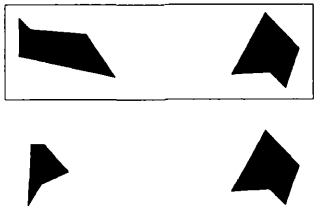
Appendix B2: The Stimuli (To Scale) Used In Set 1 Verbal And Spatial Paired Association Sections (See Pages 421-423, For An Example Of The Items At Full Size).

VERBAL PAIRED ASSOCIATION			
STUDY PHASE	1) **CHILD - CREDIT**	2) **SCHOOL - SIN**	3) **SITUATION - ACCORDING**
STUDY PHASE CONT.	4) **DAY - ENTRANCE**	5) **FEED - WHISTLE**	3) **SITUATION - ACCORDING**
TEST PHASE	1) **SCHOOL** STRETCH HIDE LIFE KNEE FAME **SIN**	2) **SITUATION** WILD HONEST SAW THREAT SIZE **ACCORDING**	3) **CHILD** PROPERTY CERTAINLY DANCE BOWL PROMISE **CREDIT**
TEST PHASE CONT.	4) **FEED** WORTHY **WHISTLE** STIR PEOPLE TRIAL YESTERDAY	5) **DAY** GARDEN INFLUENCE FIGURE **ENTRANCE** PALE ARM	
SPATIAL PAIRED ASSOCIATION			
STUDY PHASE	1) 	2) 	3) 

STUDY PHASE CONT.	4) 	5) 	
TEST PHASE	1) 	2) 	3) 
TEST PHASE CONT.	4) 	5) 	

Appendix B3: The Stimuli (To Scale) Used In Set 1 Verbal And Spatial Recognition Sections (See Pages 424-425, For An Example Of The Items At Full Size).

VERBAL RECOGNITION			
STUDY PHASE	1) **TICKET - PIECE**	2) **EMPTY - SMELL**	3) **EXCEPT - TOTAL**
STUDY PHASE CONT.	4) **SOLDIER - BIRD**	5) **PRIDE - BASE**	
TEST PHASE	1) TICKET - GIANT **TICKET - PIECE**	2) **EXCEPT - TOTAL** PIPE - EXCEPT	3) ACRE - SOLDIER **SOLDIER - BIRD**
TEST PHASE CONT.	4) **EMPTY - SMELL** EMPTY - APPROACH	5) PRIDE - PROCESS **PRIDE - BASE**	

SPATIAL RECOGNITION			
STUDY PHASE	1) 	2) 	3) 
STUDY PHASE CONT.	4) 	5) 	
TEST PHASE	1) 	2) 	3) 
TEST PHASE CONT.	4) 	5) 	

Appendix C: The Verbal And Spatial Stimuli Of Set 2 Of The New Test Of Memory.

Appendix C1: The stimuli and task demands of Set 2 verbal and spatial recall sections (See pages 398-401 for a scaled version of the items used).

VERBAL RECALL:

Study Phase: Fourteen words were presented individually, each for three seconds, during which time the subject was asked to decide whether the item was one he or she would use everyday.

Test Phase: The subject was asked to recall as many items as possible in any order.

SPATIAL RECALL:

Study Phase: Fourteen shapes were presented individually. Each comprised a regular background shape, on which was positioned a bar. In each case, the subject was required to copy the position of the bar on the background shape, using the blank shape and a replica bar, both of which were provided. (An example of the stimuli, to size, is given on pages 426-427)

Test Phase: The subject was asked to position the bar on a given background shape from memory, again having been provided with the blank shape and a replica bar. Items were studied and tested in a group of three, then four, four and then three again, that is, three items were studied and then tested, followed by the study and test phase of four items, a further four items, and then the remaining three items.

Appendix C2: The stimuli and task demands of Set 2 verbal and spatial paired association sections (See pages 402-404 for a scaled version of the items used).

VERBAL PAIRED ASSOCIATION:

Study Phase: Nine pairs of words were presented to the subject, each pair for three seconds. During this time the subject was asked to decide whether the items were words he or she would use everyday.

Test Phase: The subject was presented with the first word of a pair and asked to select the second item, from six choices.

SPATIAL PAIRED ASSOCIATION:

Study Phase: The subject was presented with nine pairs of shapes, each pair for four seconds, and asked to decide whether the items were shapes he or she could easily copy. (An example of the stimuli, to size, is given on pages 428-430).

Test Phase: The subject was given the first item of a pair and required to select the second item, from six choices.

Appendix C3: The stimuli and task demands of Set 2 verbal and spatial recognition sections (See pages 405-407 for a scaled version of the items used).

VERBAL RECOGNITION:

Study Phase: Nine pairs of words were presented to the subject, each pair for three seconds, during which the subject was asked to decide whether the items were words he or she would use everyday.

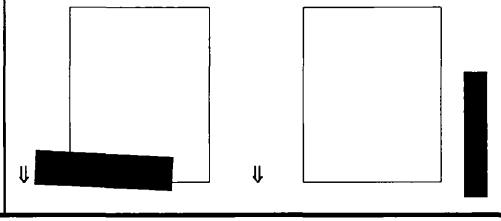
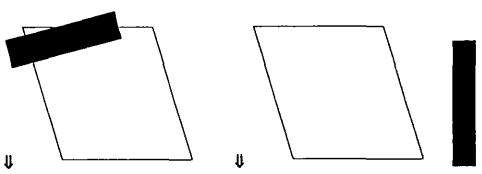
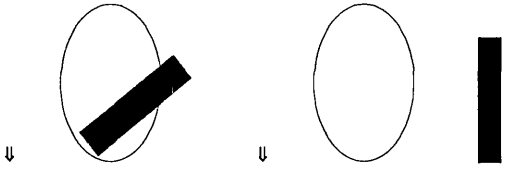
Test Phase: The subject was required to choose which of the two pairs of words had been studied previously.

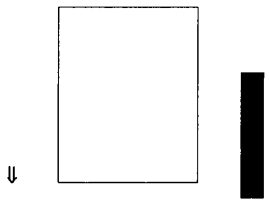
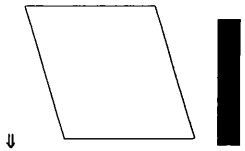
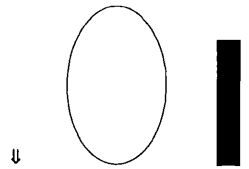
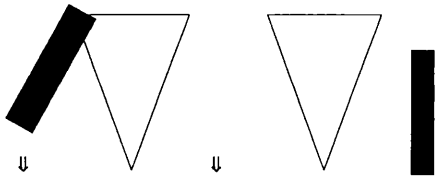
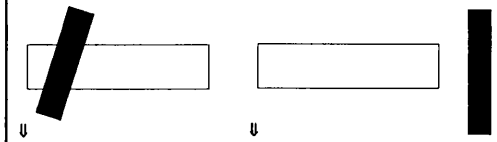
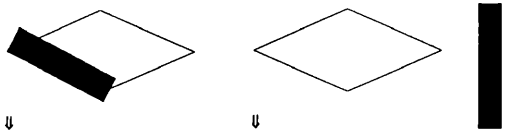
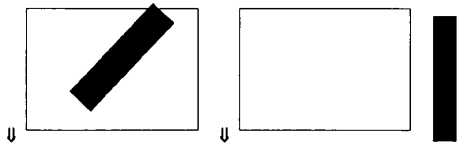
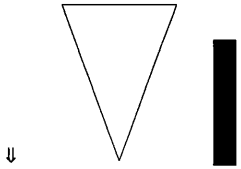
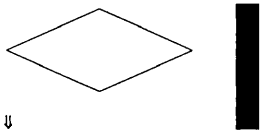
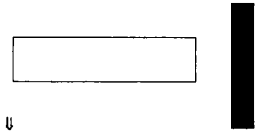
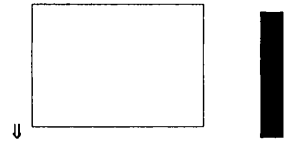
SPATIAL RECOGNITION:

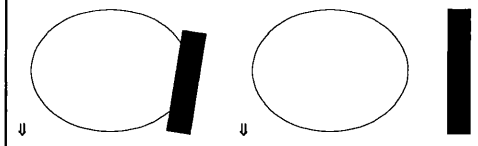
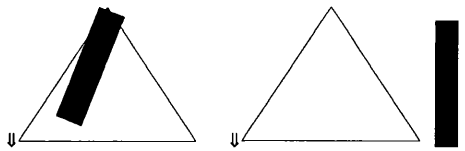
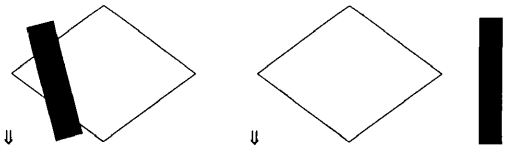
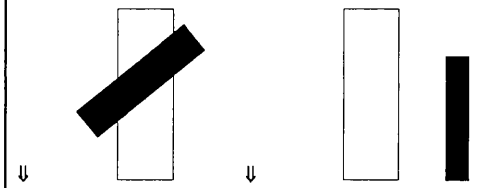
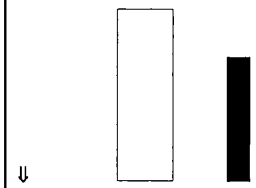
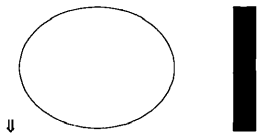
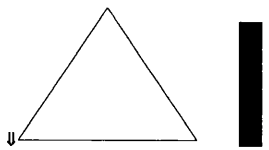
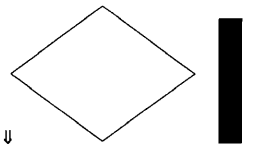
Study Phase: The subject was presented with nine pairs of shapes, each pair for four seconds, and asked to decide whether the items were shapes he or she could easily copy. (An example of the stimuli, to size, is given on pages 431-432)

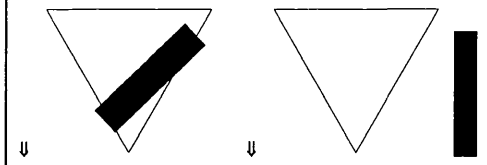
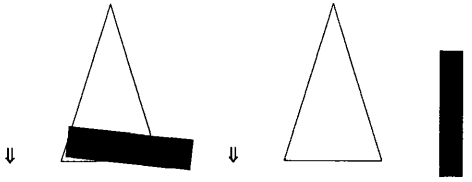
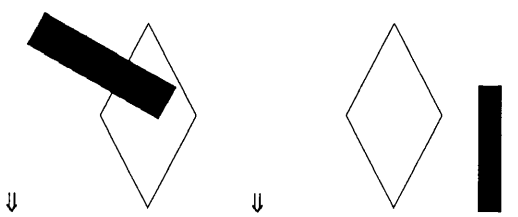
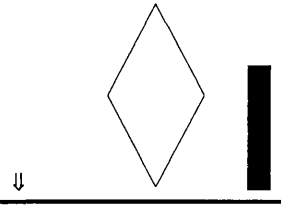
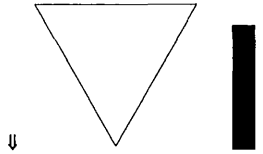
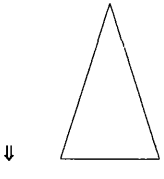
Test Phase: The subject was required to choose which of the two pairs of shapes had been studied previously.

Appendix C1: The Stimuli (To Scale) Used In Set 2 Verbal And Spatial Recall Sections (See Pages 426-427, For An Example Of The Fill Used For The Spatial Items, And The Items At Full Size).

VERBAL RECALL							
STUDY PHASE	1) **PARK**	2) **AVENUE**	3) **ADVICE**	4) **WOLF**	5) **CAST**	6) **COUNT**	7) **WHEEL**
STUDY PHASE CONT.	8) **COURT**	9) **EXACTLY**	10) **PLANE**	11) **BURN**	12) **LOVE**	13) **HALL**	14) **EVIL**
TEST PHASE	free recall						
SPATIAL RECALL							
STUDY PHASE	1) 		2) 		3) 		

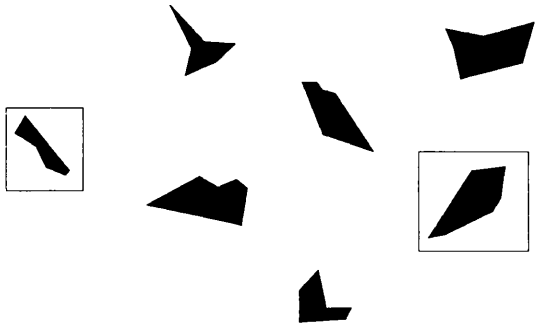
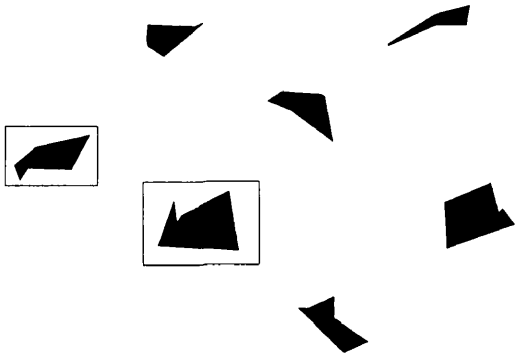
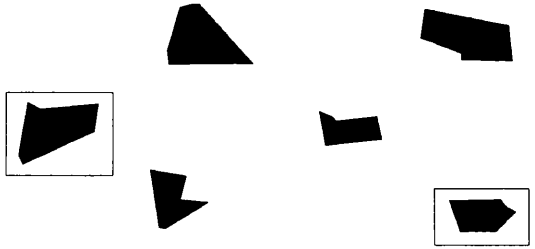
TEST PHASE	1) 	2) 	3) 
STUDY PHASE	4) 	5) 	6) 
STUDY PHASE CONT.	7) 		
TEST PHASE	4) 	5) 	6) 
			7) 

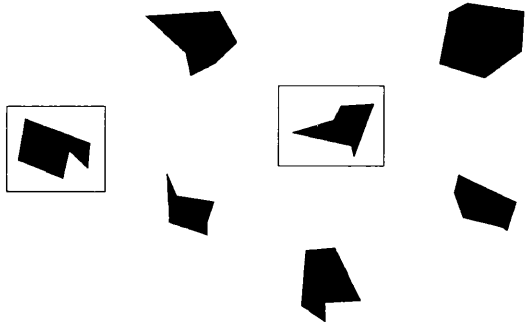
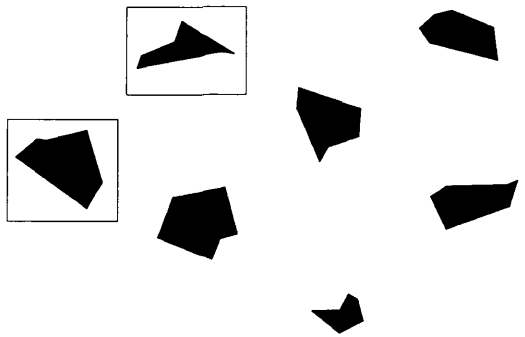
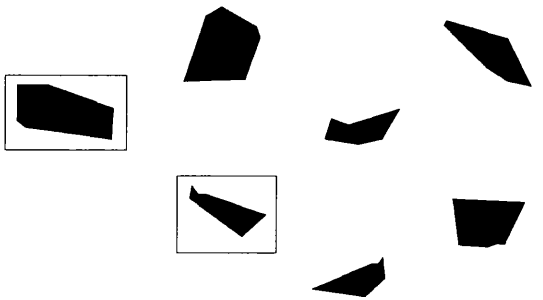
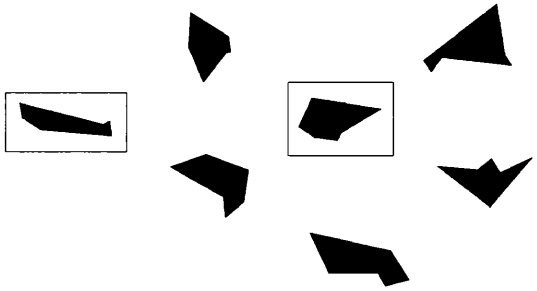
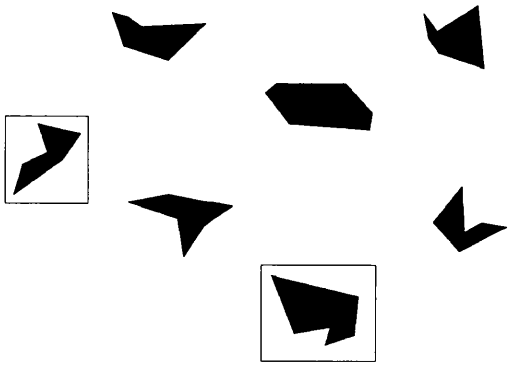
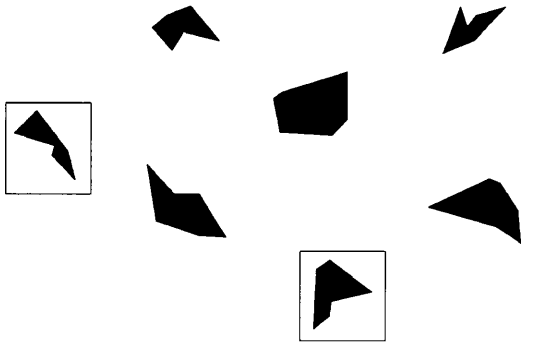
STUDY PHASE	8) 	9) 	10) 
STUDY PHASE CONT.	11) 		
TEST PHASE	8) 	9) 	10) 
			11) 

STUDY PHASE	12) 	13) 	14) 
TEST PHASE	12) 	13) 	14) 

Appendix C2: The Stimuli (To Scale) Used In Set 2 Verbal And Spatial Paired Association Sections (See Pages 428-430, For An Example Of The Items At Full Size).

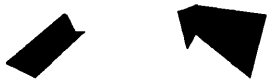
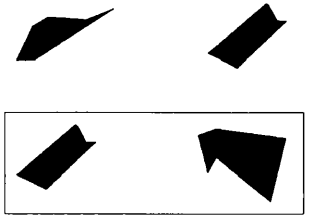
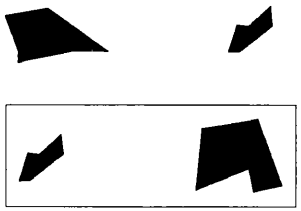
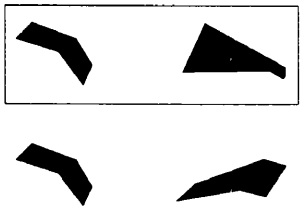
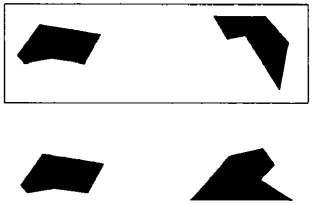
VERBAL PAIRED ASSOCIATION			
STUDY PHASE	1) **SHEEP - LIST**	2) **SERIOUS - CLOSE**	3) **PERSONAL - AFFAIR**
STUDY PHASE CONT.	4) **NOT - CHARACTER**	5) **FALL - ARMY**	6) **FILL - COTTON**
STUDY PHASE CONT.	7) **FALSE - NEAR**	8) **SEA - FREEDOM**	9) **SUPPER - SHOCK**
TEST PHASE	1) CLEAR FLOWER **FALL** **ARMY** DESK WALL COLONY	2) UNDER **FREEDOM** **SEA** POLICY TIME WHISPER VESSEL	3) POET **LIST** **SHEEP** TREASURE MILE PASSION TEAR
TEST PHASE CONT.	KINDLY LITTLE **SERIOUS** NEXT PARENT SECURE **CLOSE**	5) LORD WORLD **SUPPER** **SHOCK** ACCOUNT LATE POST	6) DEAL **AFFAIR** **PERSONAL** SLAVE FOLK ARTIST SOMETIMES

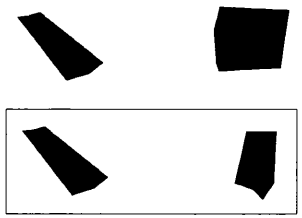
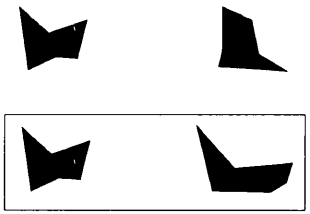
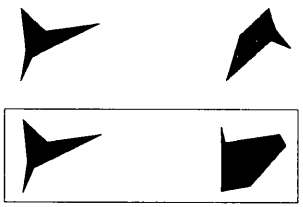
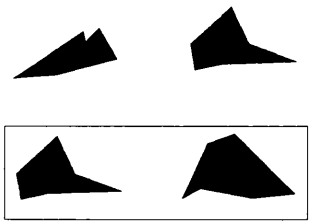
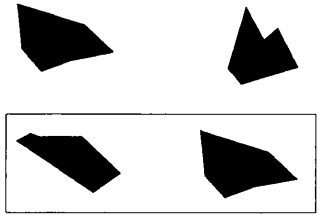
TEST PHASE CONT.	7) GREATLY STAND **NOT** TASTE CAPTAIN DOCK **CHARACTER**	8) **NEAR** RELIGIOUS **FALSE** TRAINING TROOP CAP MIDNIGHT	9) **COTTON** DRESS **FILL** SAME BREAKFAST MORE TRIBE
SPATIAL PAIRED ASSOCIATION			
STUDY PHASE	1) 	2) 	3) 
STUDY PHASE CONT.	4) 	5) 	6) 
STUDY PHASE CONT.	7) 	8) 	9) 
TEST PHASE	1) 	2) 	3) 

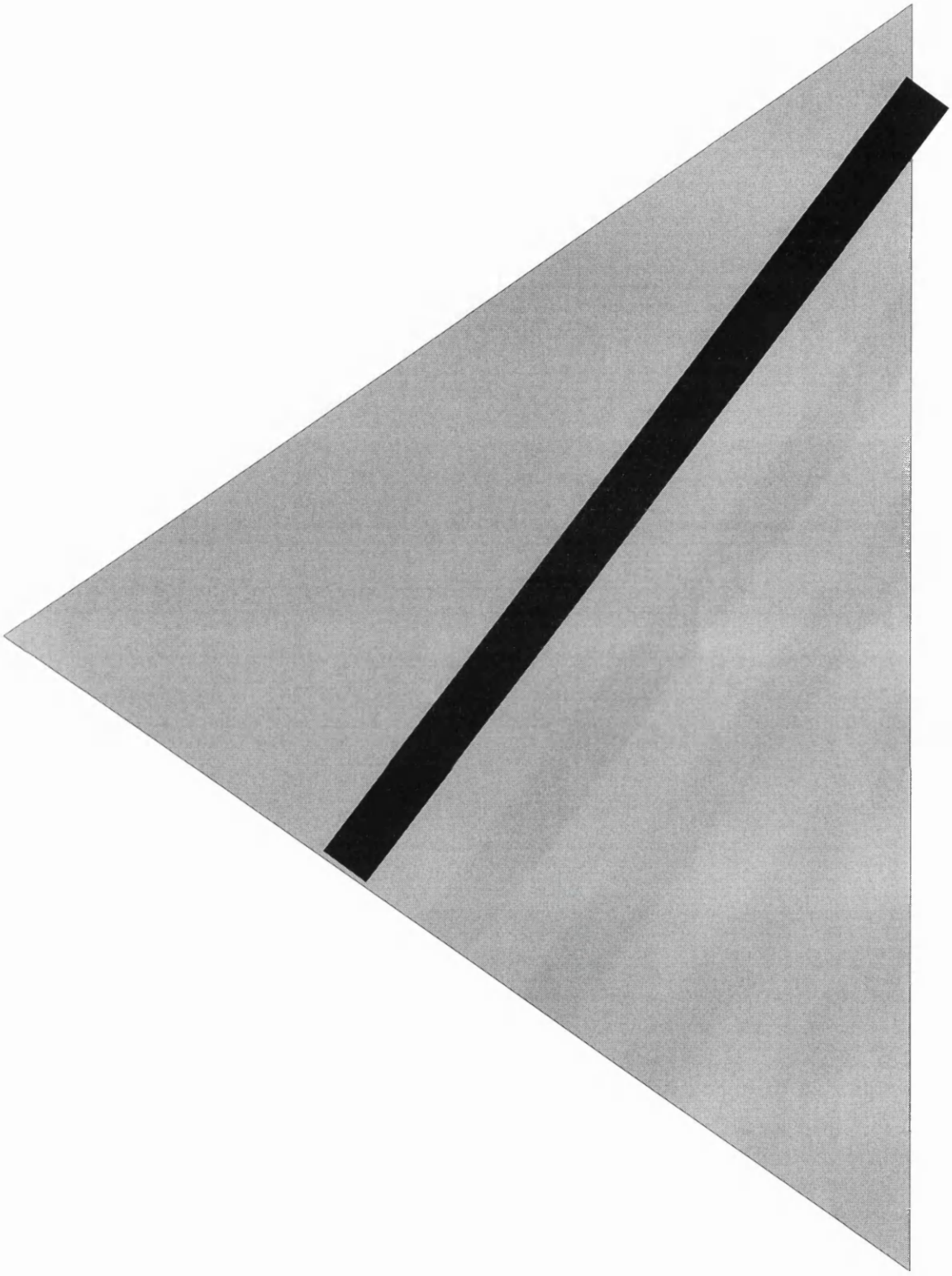
TEST PHASE CONT.	4) 	5) 	6) 
TEST PHASE CONT.	7) 	8) 	9) 

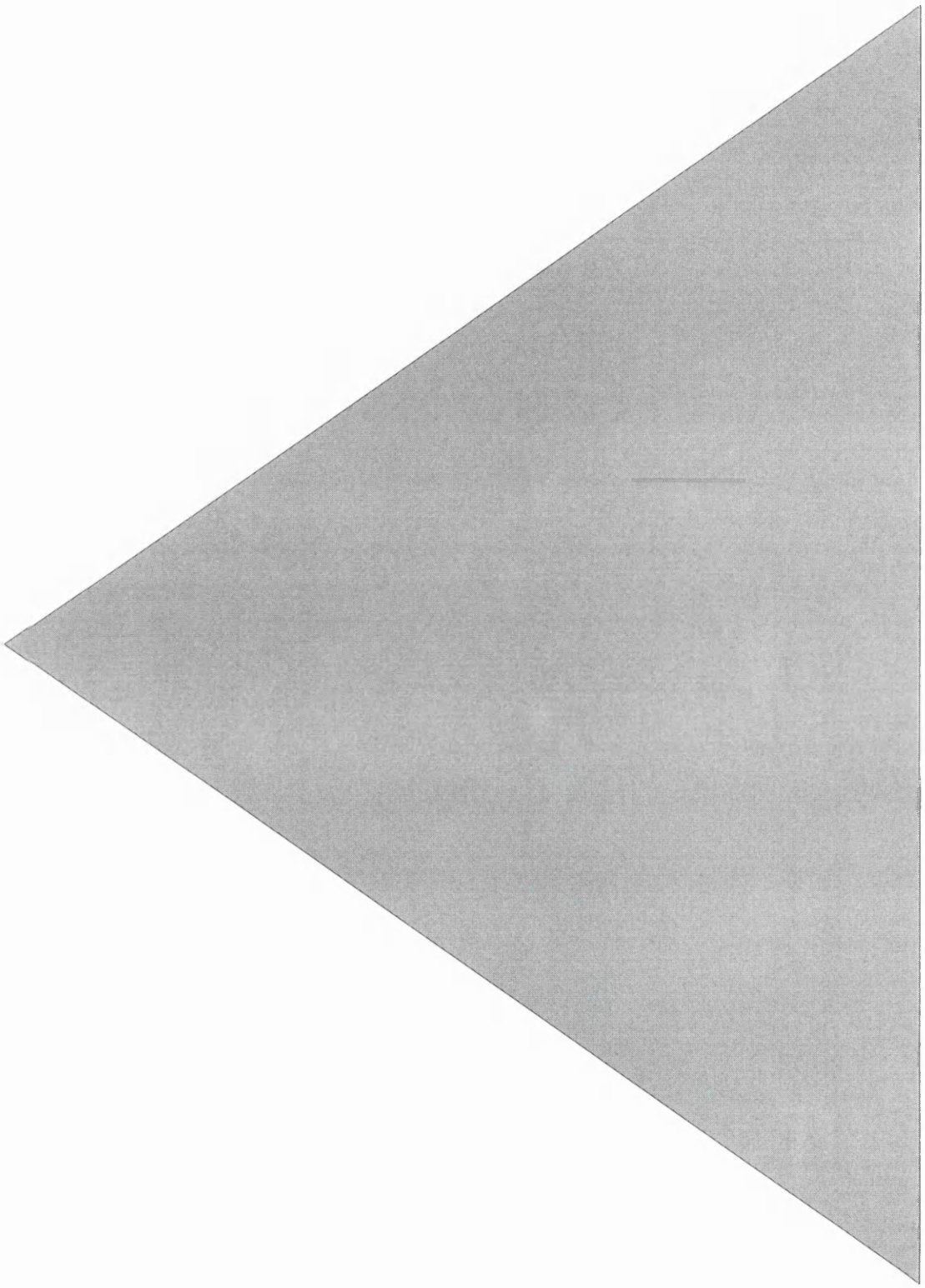
Appendix C3: The Stimuli (To Scale) Used In Set 2 Verbal And Spatial Recognition Sections (See Pages 431-432, For An Example Of The Items At Full Size).

VERBAL RECOGNITION				
STUDY PHASE	1) **POINT - DEAR**	2) **MOTOR - NOTICE**	3) **HOW - MINUTE**	4) **SHOULDER - BROWN**
STUDY PHASE CONT.	5) **POLICE - TRUTH**	6) **CHINA - SOCIETY**	7) **TELEPHONE - NATION**	8) **MONEY - BASKET**
STUDY PHASE CONT.	9) **RUIN - LESS**			
TEST PHASE	1) **MOTOR - NOTICE** NOTICE - LEAD	2) BROWN - FIX **SHOULDER - BROWN**	3) FAIRLY - CHINA **CHINA - SOCIETY**	4) **HOW - MINUTE** MINUTE - AIR
TEST PHASE CONT.	5) BASKET - ACTUALLY **MONEY - BASKET**	6) STAGE - NATION **TELEPHONE - NATION**	7) POINT - DEAR **BAG - DEAR**	8) NORTH - TRUTH **POLICE - TRUTH**

TEST PHASE CONT.	9) **RUIN - LESS** QUICK - LESS			
SPATIAL RECOGNITION				
STUDY PHASE	1) 	2) 	3) 	4) 
STUDY PHASE CONT.	5) 	6) 	7) 	8) 
STUDY PHASE CONT.	9) 			
TEST PHASE	1) 	2) 	3) 	4) 

TEST PHASE CONT.	5) 	6) 	7) 	8) 
TEST PHASE CONT.	9) 			





Appendix A2: Reproduction Of A Stimulus Item At Size; Verbal Paired Association (Study Phase) At The Task Familiarisation Stage

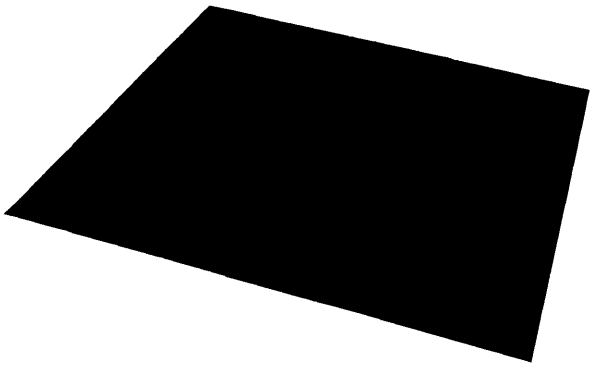
WHEAT

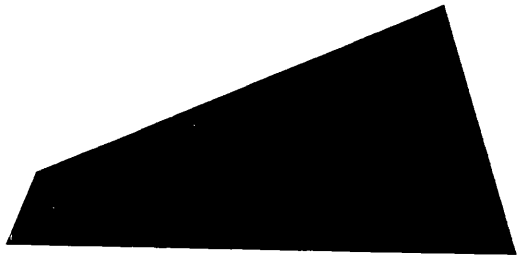
SURPRISE

Appendix A2: Reproduction Of A Stimulus Item At Size; Verbal Paired Association (Test Phase) At The Task Familiarisation Stage

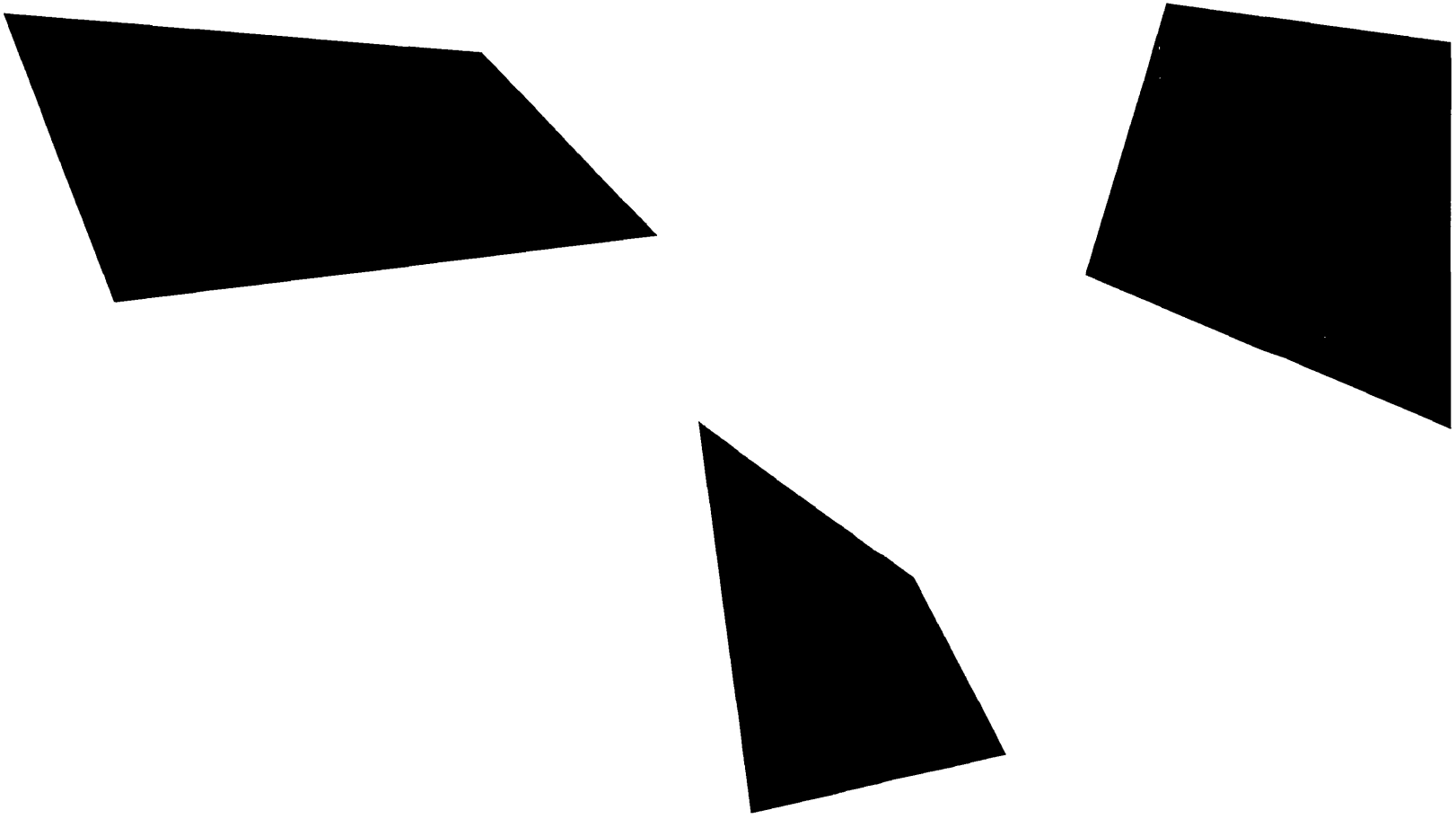
	SURPRISE	WIT
WHEAT	BOTTOM	APPEAL
	SUN	MACHINE

Appendix A2: Reproduction Of A Stimulus Item At Size; Spatial Paired Association (Study Phase) At The Task Familiarisation Stage

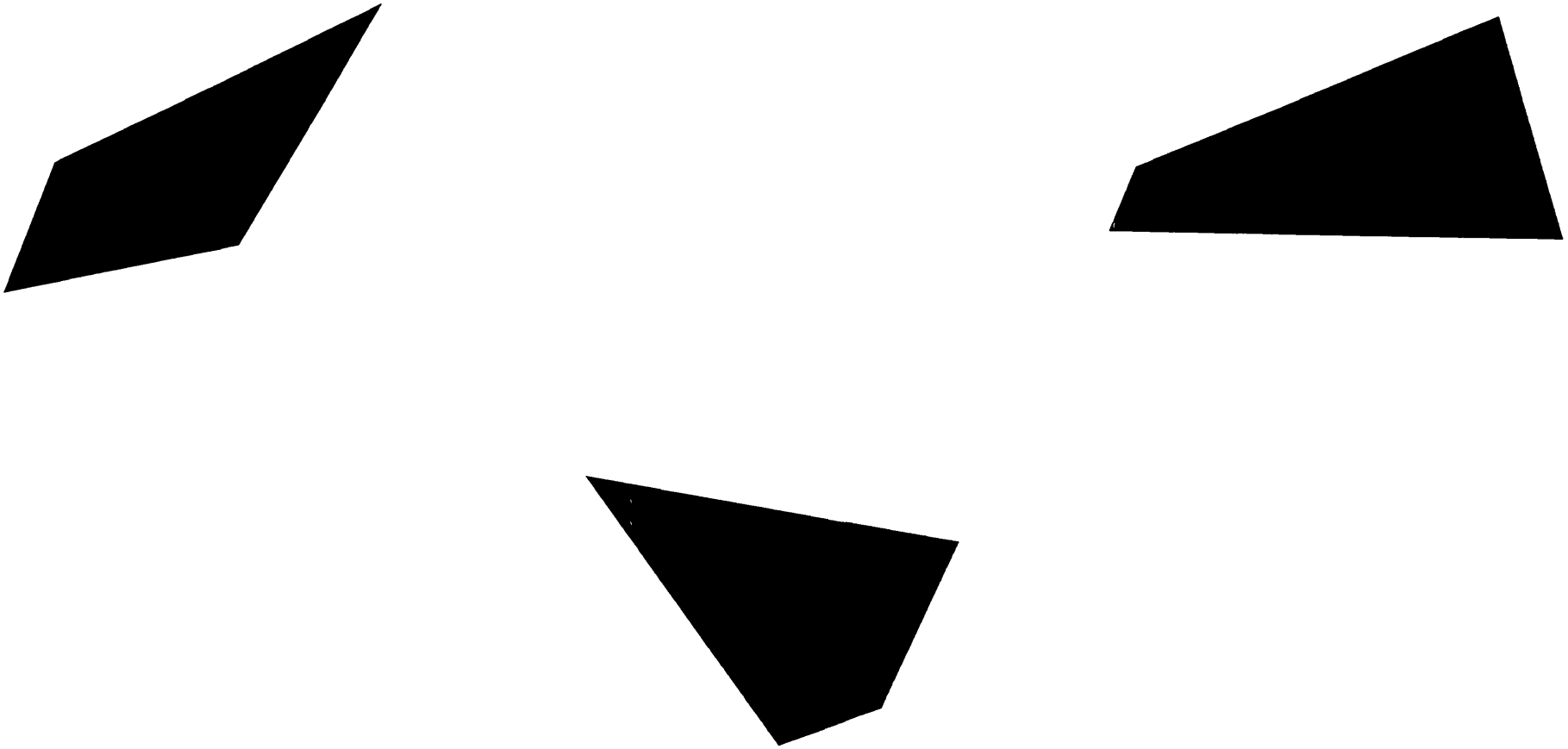




Appendix A2: Reproduction Of A Stimulus Item At Size; Spatial Paired Association (Test Phase 1) At The Task Familiarisation Stage



Appendix A2: Reproduction Of A Stimulus Item At Size; Spatial Paired Association (Test Phase 2) At The Task Familiarisation Stage



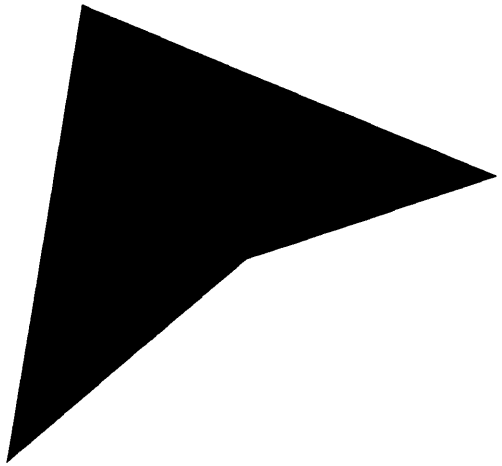
Appendix A3: Reproduction Of A Stimulus Item At Size; Verbal Recognition (Study Phase) At The Task Familiarisation Stage

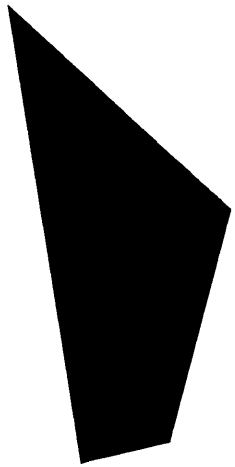
PURPOSE

TONIGHT

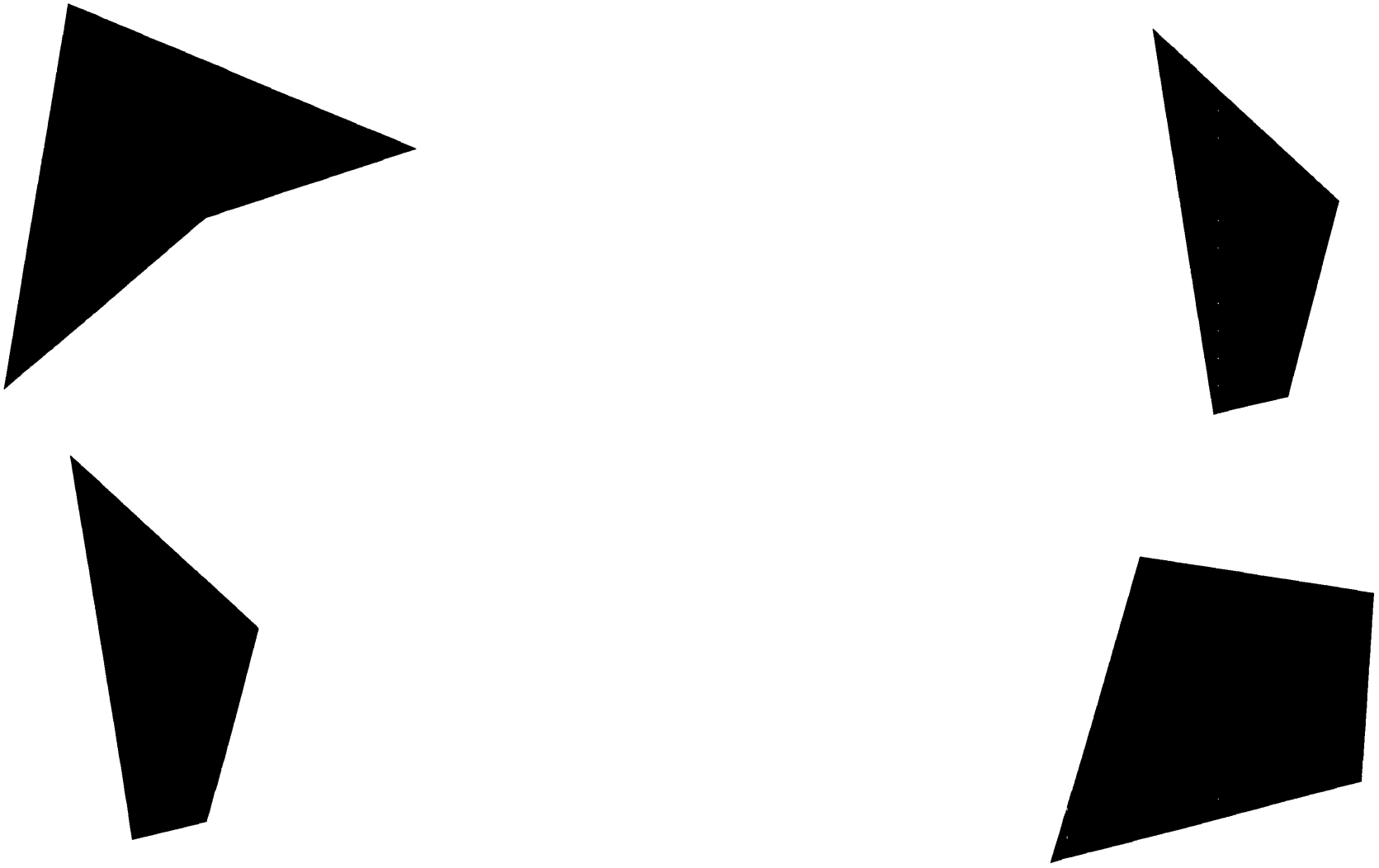
Appendix A3: Reproduction Of A Stimulus Item At Size; Verbal Recognition (Test Phase) At The Task Familiarisation Stage

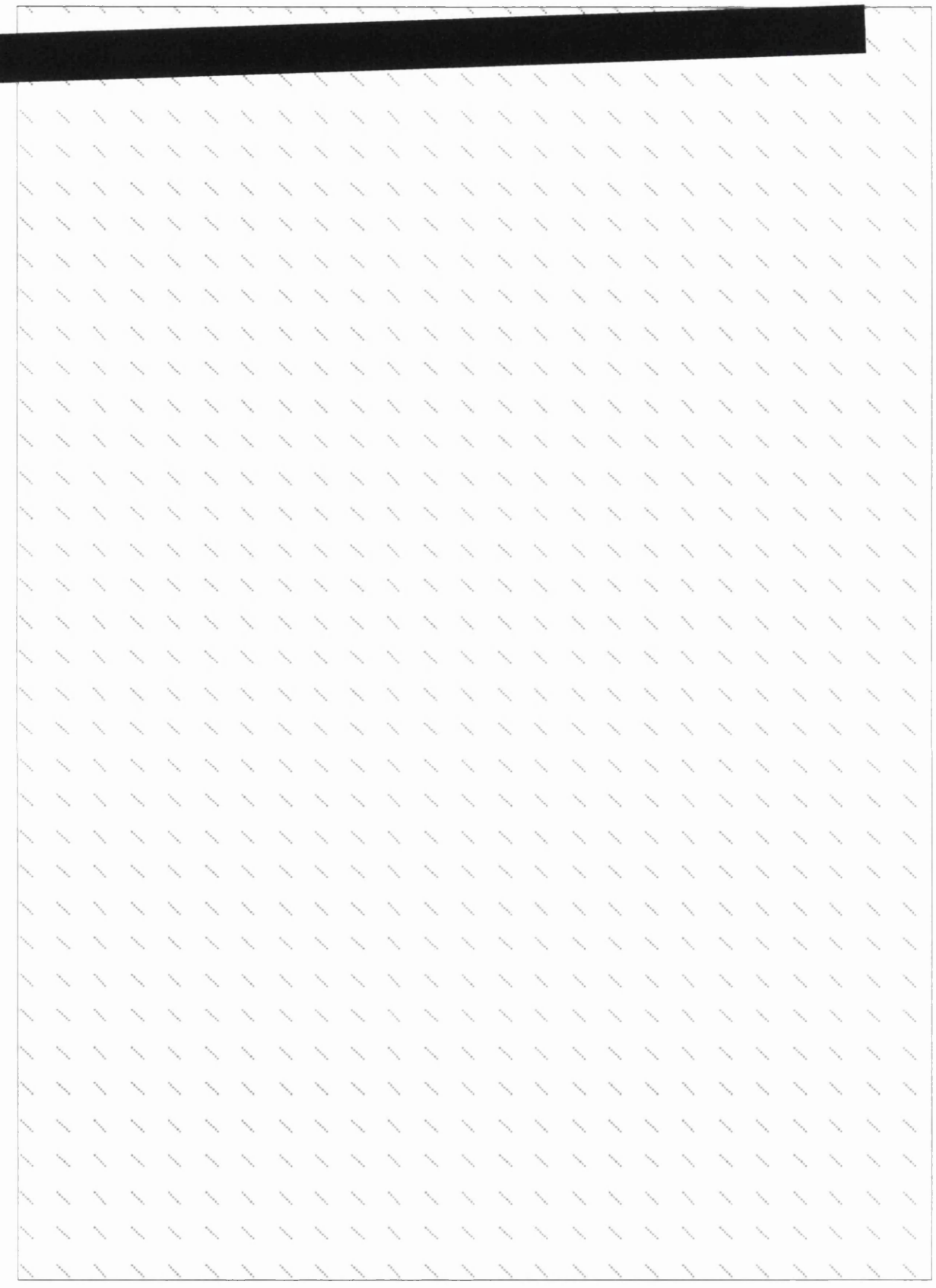
Appendix A3: Reproduction Of A Stimulus Item At Size; Spatial Recognition (Study Phase) At The Task Familiarisation Stage

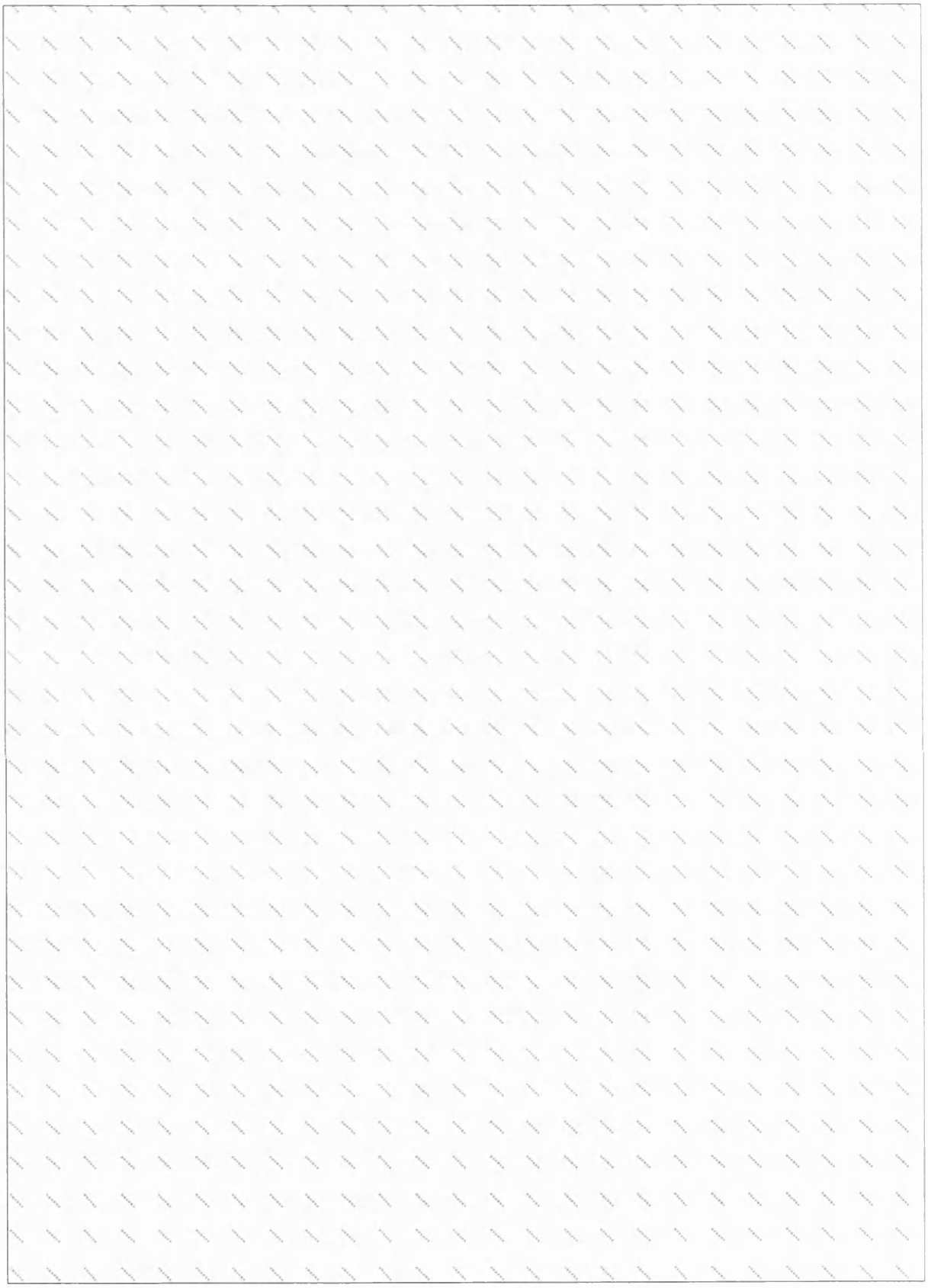


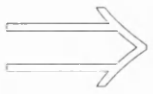


Appendix A3: Reproduction Of A Stimulus Item At Size; Spatial Recognition (Test Phase) At The Task Familiarisation Stage

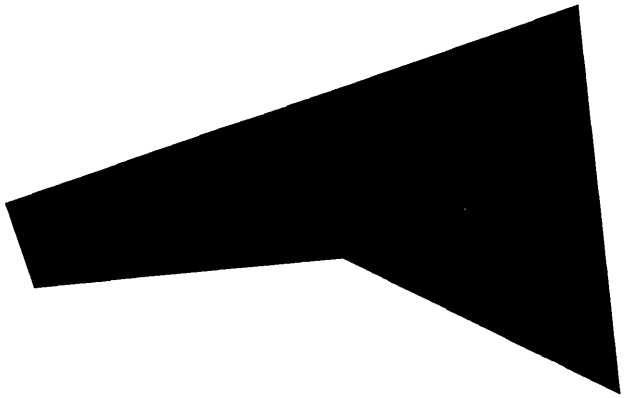


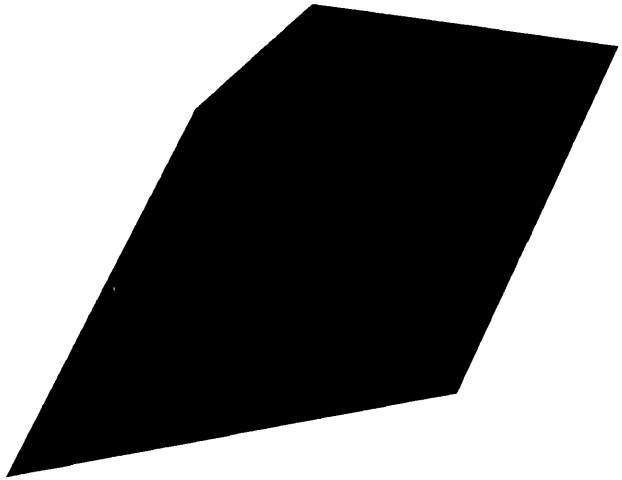




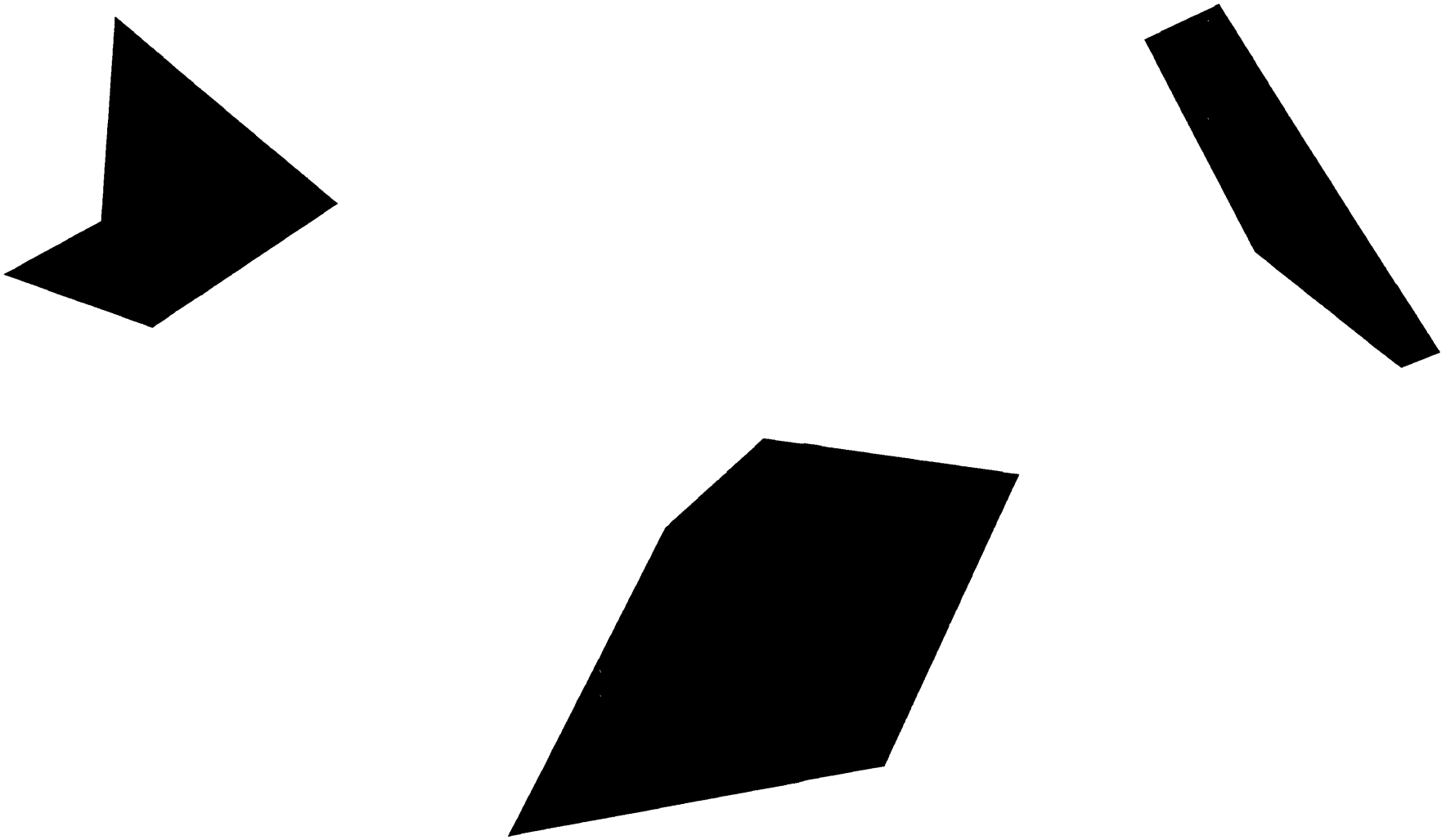


Appendix B2: Reproduction Of A Stimulus Item At Size; Set 1 Spatial Paired Association (Study Phase)

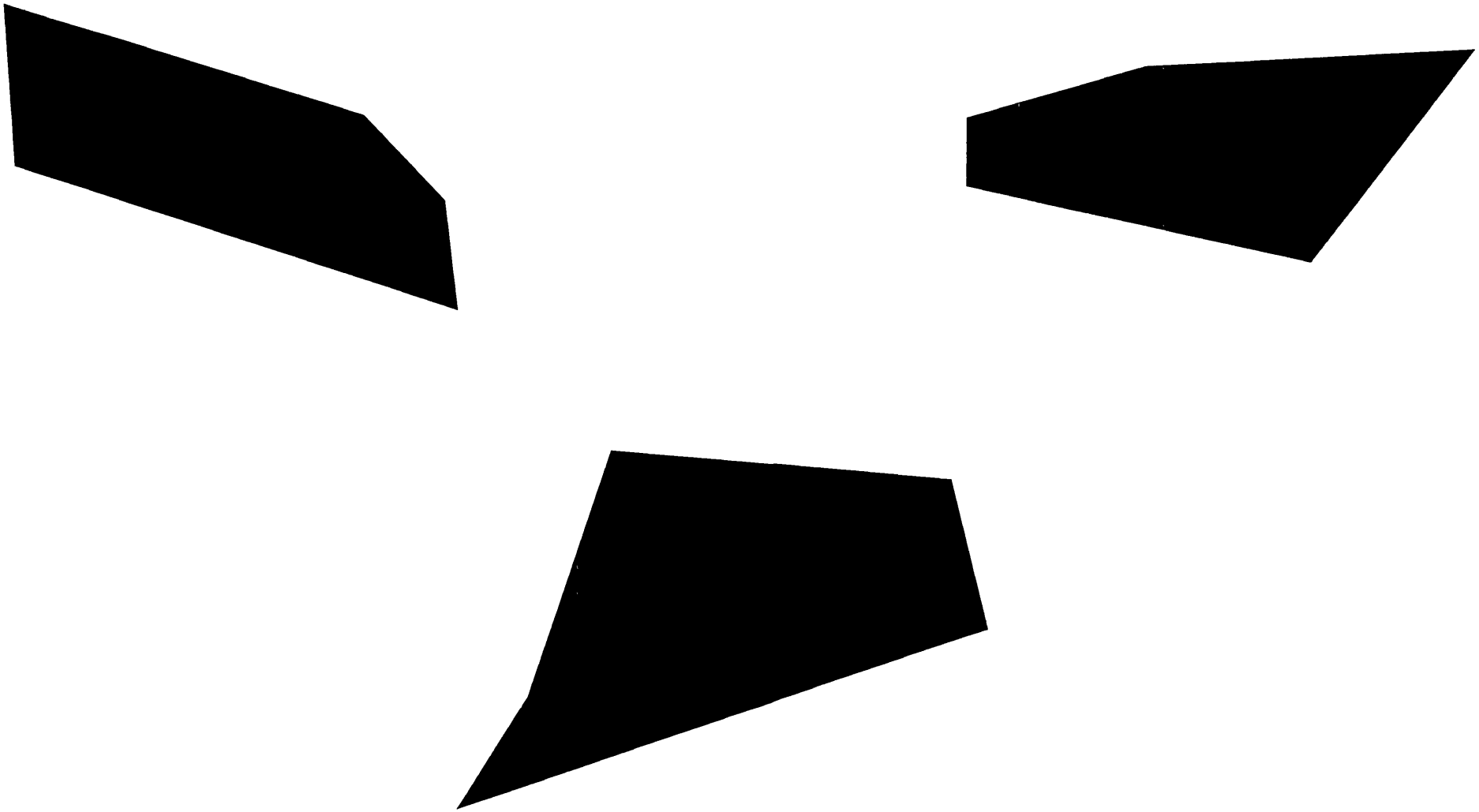




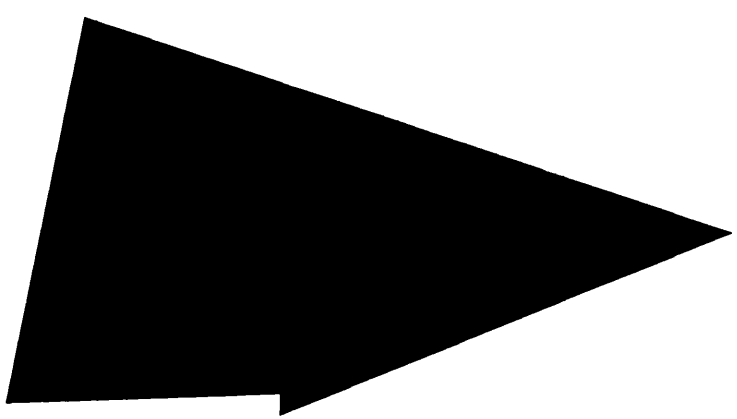
Appendix B2: Reproduction Of A Stimulus Item At Size; Set 1 Spatial Paired Association (Test Phase 1)

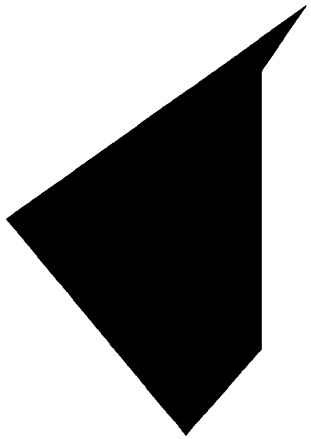


Appendix B2: Reproduction Of A Stimulus Item At Size; Set 1 Spatial Paired Association (Test Phase 2)

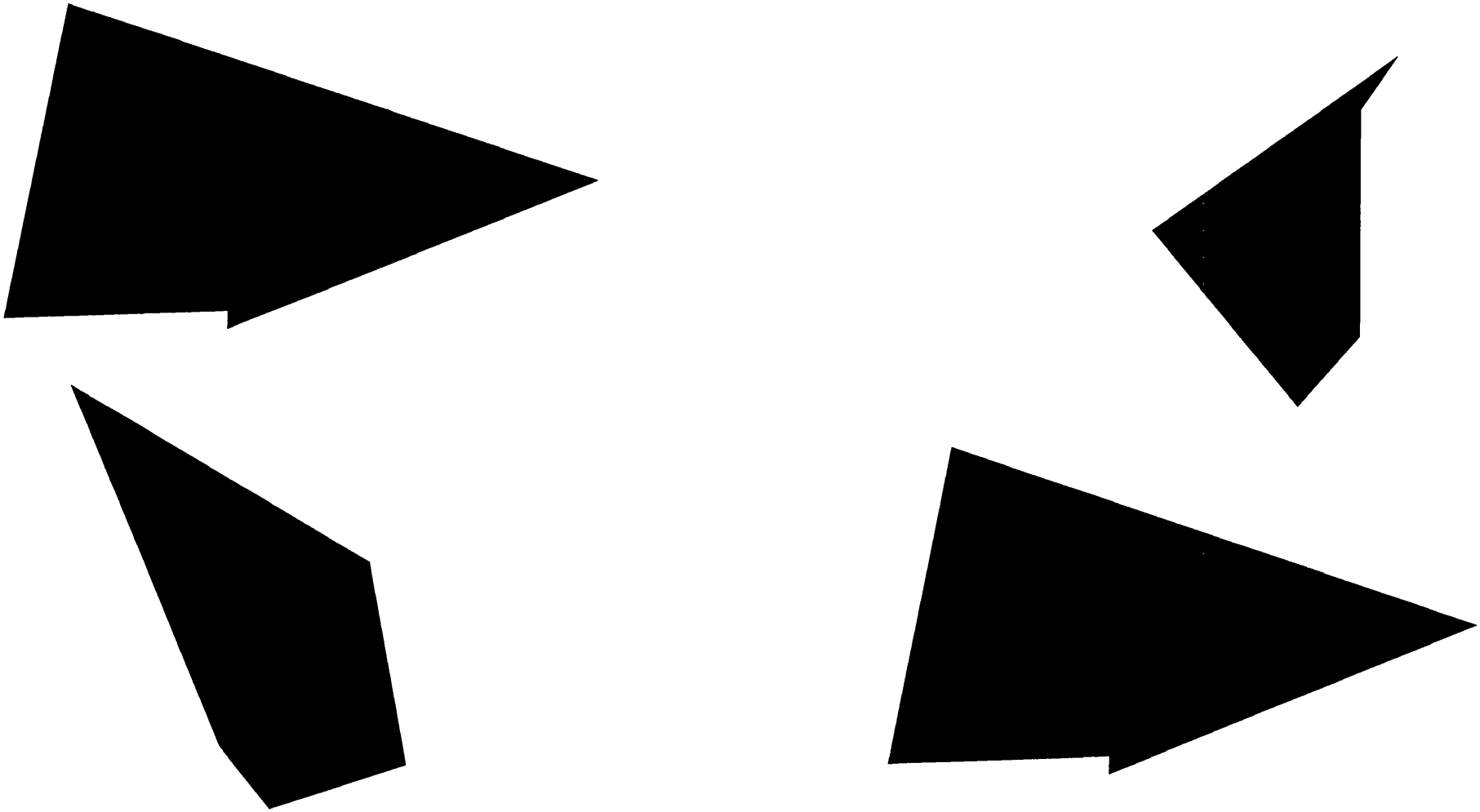


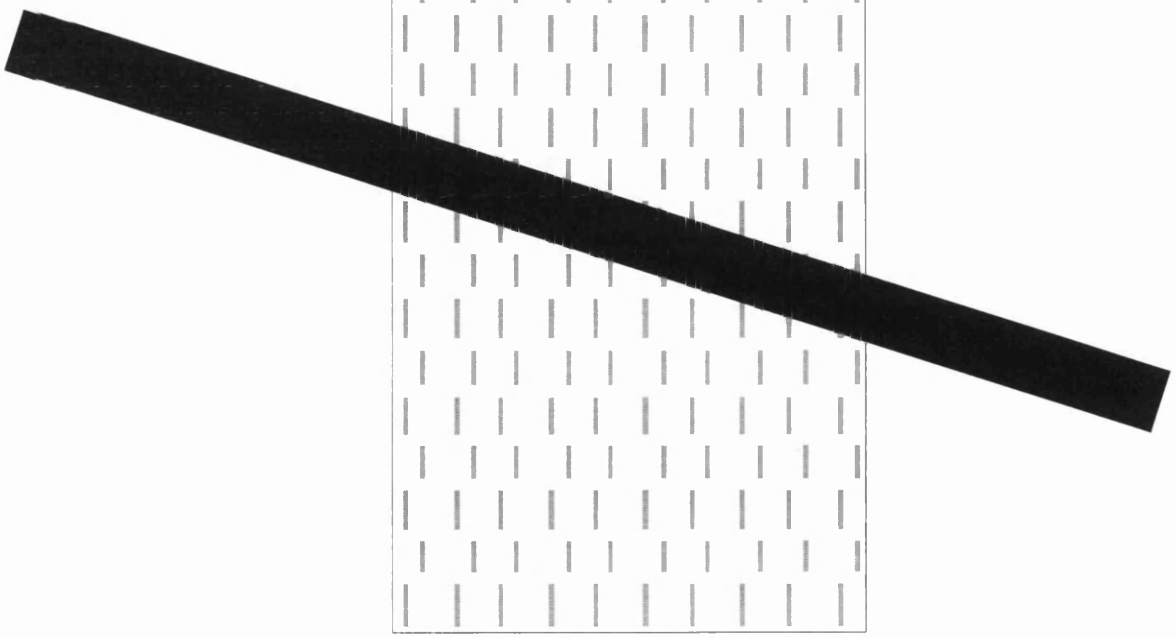
Appendix B3: Reproduction Of A Stimulus Item At Size; Set 1 Spatial Recognition (Study Phase)

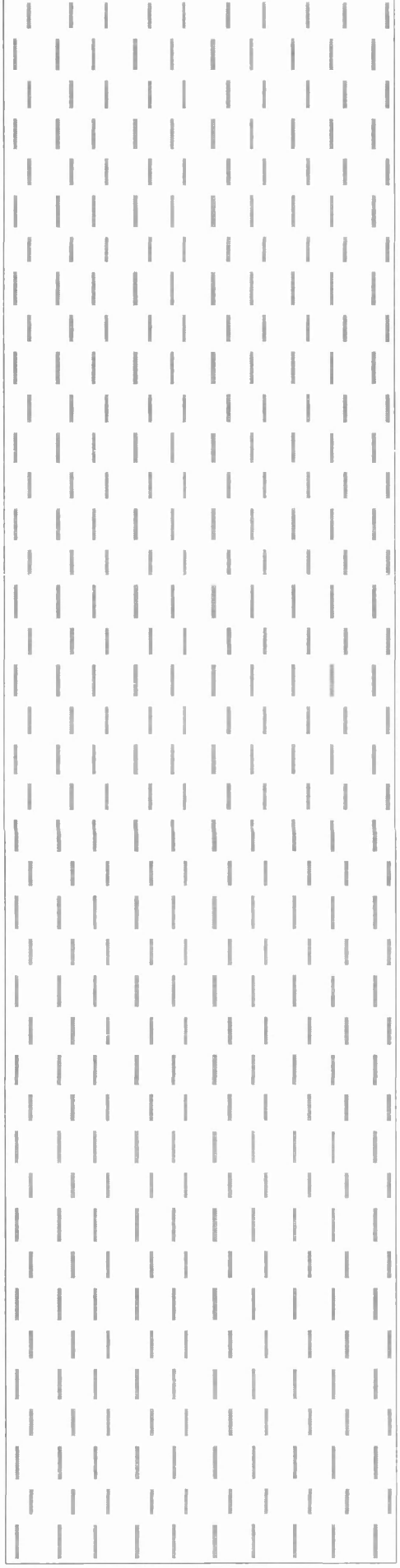




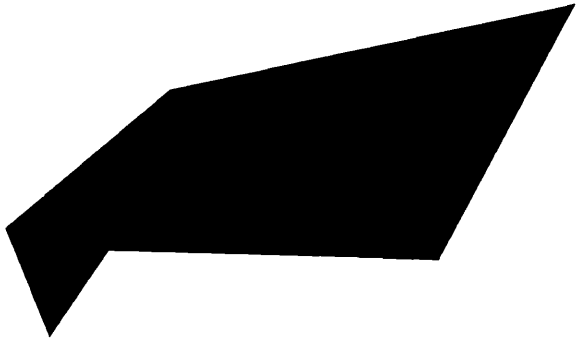
Appendix B3: Reproduction Of A Stimulus Item At Size; Set 1 Spatial Recognition (Test Phase)

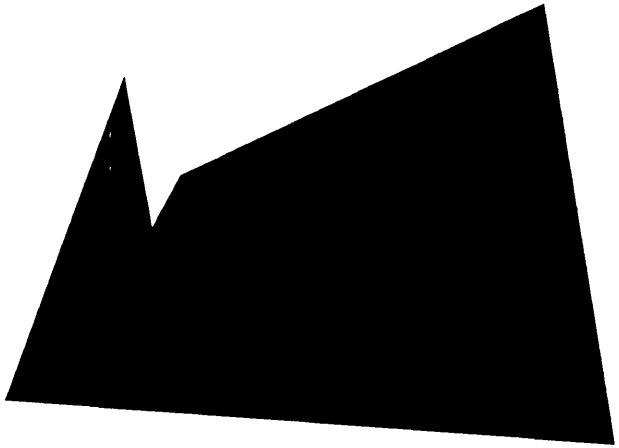




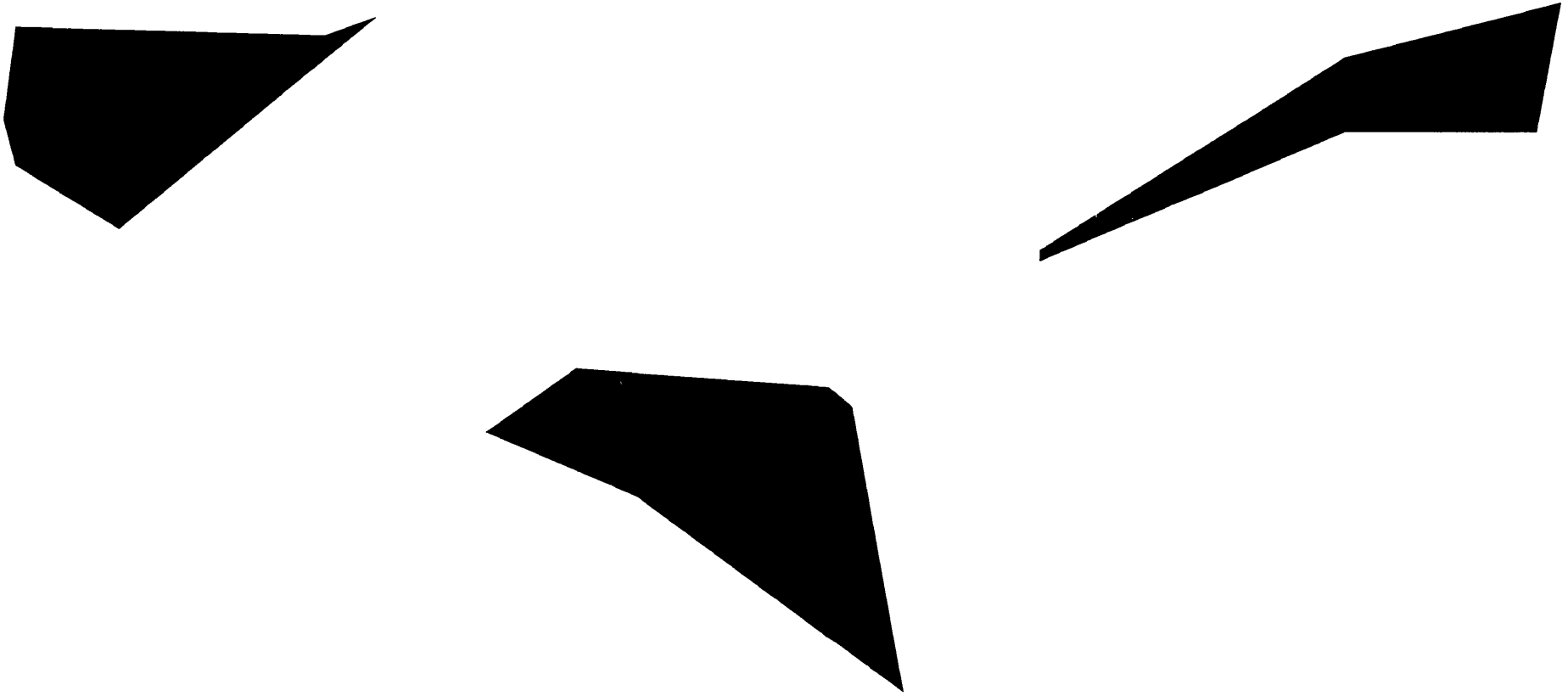


Appendix C2: Reproduction Of A Stimulus Item At Size; Set 2 Spatial Paired Association (Study Phase)

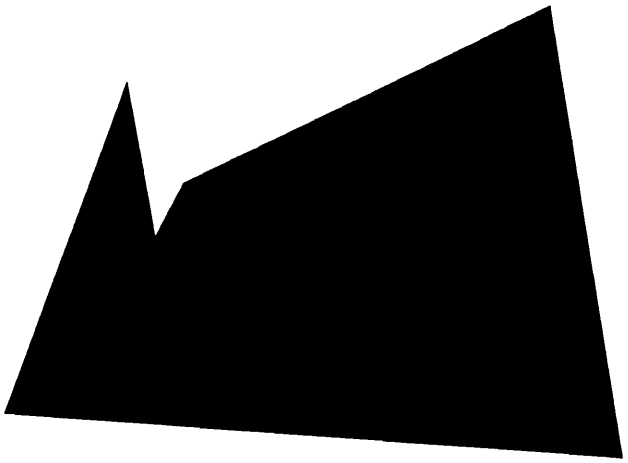


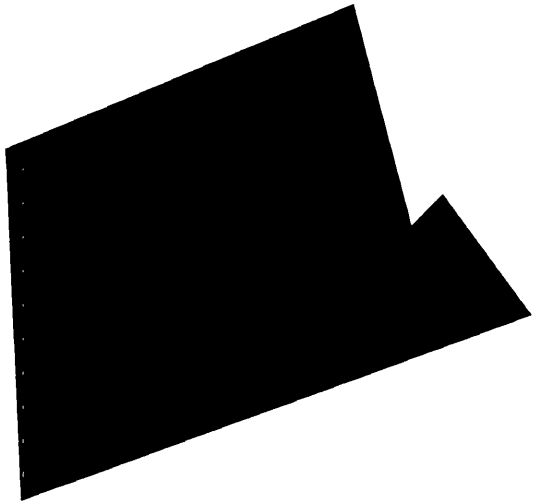


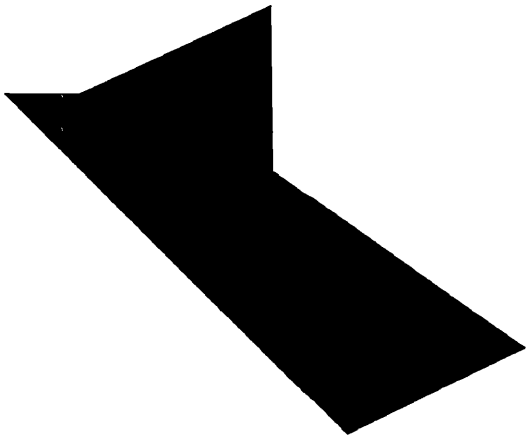
Appendix C2: Reproduction Of A Stimulus Item At Size; Set 2 Spatial Paired Association (Test Phase 1)



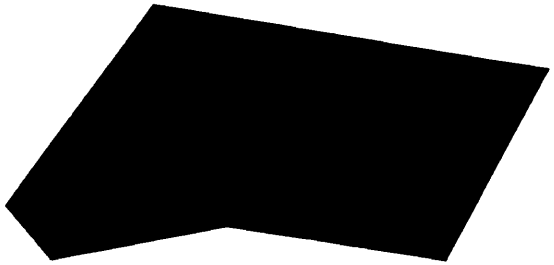
Appendix C2: Reproduction Of A Stimulus Item At Size; Set 2 Spatial Paired Association (Test Phase 2)

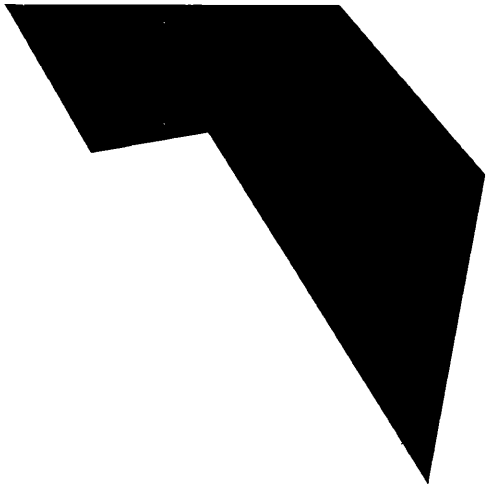




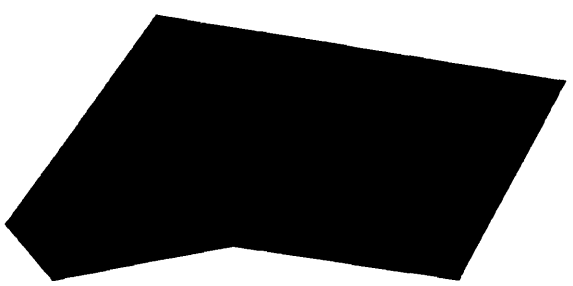


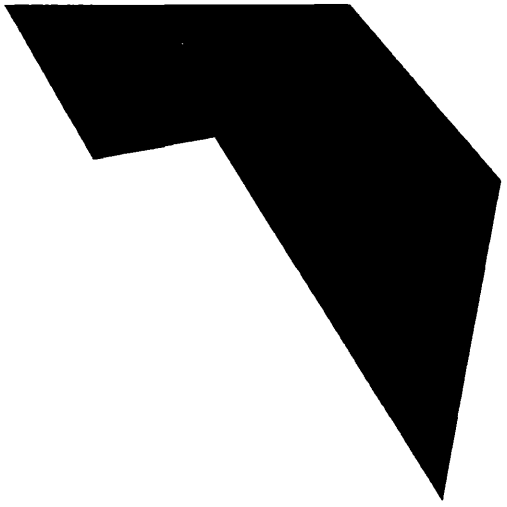
Appendix C3: Reproduction Of A Stimulus Item At Size; Set 2 Spatial Recognition (Study Phase)

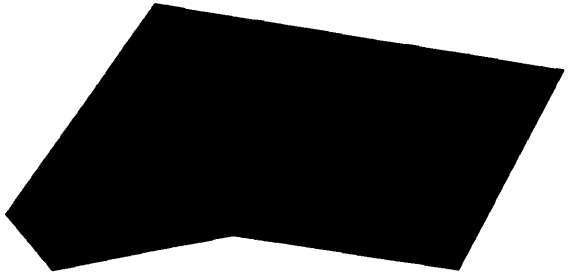


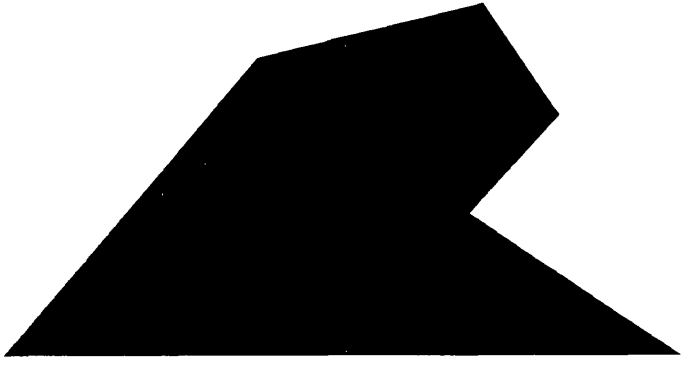


Appendix C3: Reproduction Of A Stimulus Item At Size; Set 2 Spatial Recognition (Test Phase)









Appendix D: Administration Instructions For The New Test Of Memory.

VERBAL RECALL:

Study Phase: *This is a test of memory for words. I am going to show you some words, one at a time. I do want you to try and remember them, but first of all, I want you to tell me whether they are words you would use every day. Say "yes" if they are, and "no" if they are not.*

Test Phase: *Now I want you to tell me as many words as you can remember in any order.*

VERBAL PAIRED ASSOCIATION:

Study Phase: *This is another test of memory for words. I am going to show you some pairs of words, one at a time. I do want you to try and remember them as pairs, but first of all, I want you to tell me whether they are words you would use every day. Say "yes" if they are, and "no" if they are not.*

Test Phase: *The word on the left, is the first word of one of the pairs of items you have just seen, I want you to select from the six choices, the word you think went with it, to make up the pair.*

VERBAL RECOGNITION:

Study Phase: *This is another test of memory for words. I am going to show you some pairs of words, one at a time. Again, I do want you to try and remember them as pairs, but first of all, I want you to tell me whether they are words you would use every day. Say "yes" if they are, and "no" if they are not.*

Test Phase: *In this task, I want you to indicate which pair of words you have just seen, the top pair or the bottom pair.*

SPATIAL RECALL:

Study Phase: *This is a test of spatial memory. I am going to show you some designs, one at a time, and I want you to try and remember the position of the bar on the given background shape. First of all, however, I want you just to copy the position of the bar, on the blank shape in front of you, using this bar (indicate the bar).*

Test Phase: *Now I want you to position the bar on the given shape, from memory.*

SPATIAL PAIRED ASSOCIATION:

Study Phase: *This is another test of spatial memory. I am going to show you some pairs of shapes, one at a time. I do want you to try and remember them as pairs, but first of all, I want you to tell me whether they are shapes you could easily copy. Say "yes" if they are, and "no" if they are not.*

Test Phase: *The shape on the left, is the first shape, the left hand one, (indicate by pointing to the left of the page) of one of the pairs of items you have just seen, I want you to choose from the six choices, the shape you think went with it, to make up the pair.*

SPATIAL RECOGNITION:

Study Phase: *This is another test of spatial memory. I am going to show you some pairs of shapes, one at a time. Again, I do want you to try and remember them as pairs, but first of all, I want you to tell me whether they are shapes you could easily copy. Say "yes" if they are, and "no" if they are not.*

Test Phase: *In this task, I want you to indicate which pair of shapes you have just seen, the top pair or the bottom pair.*

Appendix E: Calculating Chance Scores For The Paired Association And Recognition Sections Of The New Test Of Memory

This method assumes that the probability of getting an item correct is independent of whether or not any other item is answered correctly. Taking all items together and using the binomial distribution: $P(y): [n ! / y ! (n - y)] \; p^{y} (1 - p)^{n-y}$

PAIRED ASSOCIATION:

For the Paired Association Sections, as there are six choices, only one of which is correct, the probability of answering one item correctly is $p = 0.16667$

For Task Familiarisation Paired Association Sections there are three items, therefore the range of scores is from 0 to 3:

$P(y = 0): [3! / 0 ! (3 - 0)] \; 0.16667^{0} (1 - 0.16667)^{3-0} = 0.5787$

$P(y = 1): [3! / 1 ! (3 - 1)] \; 0.16667^{1} (1 - 0.16667)^{3-1} = 0.3472$

$P(y = 2): [3! / 2 ! (3 - 2)] \; 0.16667^{2} (1 - 0.16667)^{3-2} = 0.0694$

$P(y = 3): [3! / 3 ! (3 - 3)] \; 0.16667^{3} (1 - 0.16667)^{3-3} = 0.0046$

Expected Score By Chance:

$0 . P(y = 0) + 1 . P(y = 1) + 2 . P(y = 2) + 3 . P(y = 3) = 0.500$

For Set 1 Paired Association Sections there are five items, therefore the range of scores is from 0 to 5:

$P(y = 0): [5! / 0 ! (5 - 0)] \; 0.16667^{0} (1 - 0.16667)^{5-0} = 0.4018$

$P(y = 1): [5! / 1 ! (5 - 1)] \; 0.16667^{1} (1 - 0.16667)^{5-1} = 0.4018$

$P(y = 2): [5! / 2 ! (5 - 2)] \; 0.16667^{2} (1 - 0.16667)^{5-2} = 0.1607$

$P(y = 3): [5! / 3 ! (5 - 3)] \; 0.16667^{3} (1 - 0.16667)^{5-3} = 0.0322$

$P(y = 4): [5! / 4 ! (5 - 4)] \; 0.16667^{4} (1 - 0.16667)^{5-4} = 0.0032$

$P(y = 5): [5! / 5 ! (5 - 5)] \; 0.16667^{5} (1 - 0.16667)^{5-5} = 0.0001$

Expected Score By Chance:

$0 . P(y = 0) + 1 . P(y = 1) + 2 . P(y = 2) + 3 . P(y = 3) + 4 . P(y = 4) + 5 . P(y = 5) =$ 0.833

For Set 2 Paired Association Sections there are nine items, therefore the range of scores is from 0 to 9:

$P(y = 0)$: $[9! / 0!(9 - 0)]\ 0.16667^{0} (1 - 0.16667)^{9-0} = 0.1937$

$P(y = 1)$: $[9! / 1!(9 - 1)]\ 0.16667^{1} (1 - 0.16667)^{9-1} = 0.3488$

$P(y = 2)$: $[9! / 2!(9 - 2)]\ 0.16667^{2} (1 - 0.16667)^{9-2} = 0.2790$

$P(y = 3)$: $[9! / 3!(9 - 3)]\ 0.16667^{3} (1 - 0.16667)^{9-3} = 0.1302$

$P(y = 4)$: $[9! / 4!(9 - 4)]\ 0.16667^{4} (1 - 0.16667)^{9-4} = 0.0391$

$P(y = 5)$: $[9! / 5!(9 - 5)]\ 0.16667^{5} (1 - 0.16667)^{9-5} = 0.0078$

$P(y = 6)$: $[9! / 5!(9 - 6)]\ 0.16667^{6} (1 - 0.16667)^{9-6} = 0.0010$

$P(y = 7)$: $[9! / 7!(9 - 7)]\ 0.16667^{7} (1 - 0.16667)^{9-7} = 8.931 \times 10^{-5}$

$P(y = 8)$: $[9! / 8!(9 - 8)]\ 0.16667^{8} (1 - 0.16667)^{9-8} = 4.466 \times 10^{-6}$

$P(y = 9)$: $[9! / 9!(9 - 9)]\ 0.16667^{9} (1 - 0.16667)^{9-9} = 9.9 \times 10^{-8}$

Expected Score By Chance:

$0 . P(y = 0) + 1 . P(y = 1) + 2 . P(y = 2) + 3 . P(y = 3) + 4 . P(y = 4) + 5 . P(y = 5) + 6 . P(y = 6) + 7 . P(y = 7) + 8 . P(y = 8) + 9 . P(y = 9) = 1.500$

RECOGNITION:

For the Recognition Sections, as there are two choices, only one of which is correct, the probability of answering one item correctly is $P = 0.5$

For Task Familiarisation Recognition Sections there are three items, therefore the range of scores is from 0 to 3:

$P(y = 0)$: $[3! / 0!(3 - 0)]\ 0.5^{0} (1 - 0.5)^{3-0} = 0.1250$

$P(y = 1)$: $[3! / 1!(3 - 1)]\ 0.5^{1} (1 - 0.5)^{3-1} = 0.3750$

$P(y = 2)$: $[3! / 2!(3 - 2)]\ 0.5^{2} (1 - 0.5)^{3-2} = 0.3750$

$P(y = 3)$: $[3! / 3!(3 - 3)]\ 0.5^{3} (1 - 0.5)^{3-3} = 0.1250$

Expected Score By Chance:

$0 . P(y = 0) + 1 . P(y = 1) + 2 . P(y = 2) + 3 . P(y = 3) = 1.500$

For Set 1 Recognition Sections there are five items, therefore the range of scores is from 0 to 5:

$P(y = 0)$: $[5! / 0! (5 - 0)]\ 0.5^{0} (1 - 0.5)^{5-0} = 0.03125$

$P(y = 1)$: $[5! / 1! (5 - 1)]\ 0.5^{1} (1 - 0.5)^{5-1} = 0.15625$

$P(y = 2)$: $[5! / 2! (5 - 2)]\ 0.5^{2} (1 - 0.5)^{5-2} = 0.31250$

$P(y = 3)$: $[5! / 3! (5 - 3)]\ 0.5^{3} (1 - 0.5)^{5-3} = 0.31250$

$P(y = 4)$: $[5! / 4! (5 - 4)]\ 0.5^{4} (1 - 0.5)^{5-4} = 0.15625$

$P(y = 5)$: $[5! / 5! (5 - 5)]\ 0.5^{5} (1 - 0.5)^{5-5} = 0.03125$

Expected Score By Chance:

$0 . P(y = 0) + 1 . P(y = 1) + 2 . P(y = 2) + 3 . P(y = 3) + 4 . P(y = 4) + 5 . P(y = 5) = 2.500$

For Set 2 Recognition Sections there are nine items, therefore the range of scores is from 0 to 9:

$P(y = 0)$: $[9! / 0! (9 - 0)]\ 0.5^{0} (1 - 0.5)^{9-0} = 0.0020$

$P(y = 1)$: $[9! / 1! (9 - 1)]\ 0.5^{1} (1 - 0.5)^{9-1} = 0.0176$

$P(y = 2)$: $[9! / 2! (9 - 2)]\ 0.5^{2} (1 - 0.5)^{9-2} = 0.0703$

$P(y = 3)$: $[9! / 3! (9 - 3)]\ 0.5^{3} (1 - 0.5)^{9-3} = 0.1641$

$P(y = 4)$: $[9! / 4! (9 - 4)]\ 0.5^{4} (1 - 0.5)^{9-4} = 0.2461$

$P(y = 5)$: $[9! / 5! (9 - 5)]\ 0.5^{5} (1 - 0.5)^{9-5} = 0.2461$

$P(y = 6)$: $[9! / 5! (9 - 6)]\ 0.5^{6} (1 - 0.5)^{9-6} = 0.1641$

$P(y = 7)$: $[9! / 7! (9 - 7)]\ 0.5^{7} (1 - 0.5)^{9-7} = 0.0703$

$P(y = 8)$: $[9! / 8! (9 - 8)]\ 0.5^{8} (1 - 0.5)^{9-8} = 0.0176$

$P(y = 9)$: $[9! / 9! (9 - 9)]\ 0.5^{9} (1 - 0.5)^{9-9} = 0.0020$

Expected Score By Chance:

$0 . P(y = 0) + 1 . P(y = 1) + 2 . P(y = 2) + 3 . P(y = 3) + 4 . P(y = 4) + 5 . P(y = 5) + 6 . P(y = 6) + 7 . P(y = 7) + 8 . P(y = 8) + 9 . P(y = 9) = 4.500$

Appendix F: A List Of The Companies And Organisations From Which Healthy Volunteers Were Recruited.

1) **Automobile Association,** Norfolk House, Priestly Rd., Basingstoke, RG24 9NY.
2) **Binder Hamlyn, Andersen Worldwide,** 20 Old Bailey, LONDON, EC4M 7BH.
3) **Body Shop International Plc.,** Watersmead, Littlehampton, W. SUSSEX, BN17 6LS.
4) **J. Sainsbury Plc.,** Stamford House, Stamford St., LONDON, SE1 9LL; Norwich House, 9-11 Streatham High Rd., LONDON, SW16 1DU.
5) **The London Borough Of Hammersmith & Fulham,** Hammersmith Town Hall, King St., Hammersmith, LONDON, W6 9LU.
6) **Lucas Bryce,** Hatherley Lane, Cheltenham, GLOUCESTER, GL51 0EU.
7) **McDonald's Restaurants Ltd.,** 11-59 High Rd., E. Finchley, LONDON, N2 8AW.
8) **Mary Ward Centre,** 42 Queen Square, LONDON, WC1N 3AQ.
9) **Melbourne Women's Institute,** Melbourne, Derby, DERBYSHIRE, DE7.
10) **Strete Social Club,** Strete, Dartmouth, S. DEVON, TQ6.
11) **Total Oil Great Britain Ltd.,** 33 Cavendish Sq., LONDON, W1M 0EX.
12) **Virgin Our Price,** Kew House, Capital Interchange Way, Brentford, MIDDLESEX, TW8 0EX.
13) **West Kent Women's Institute,** Lamberhurst, Tunbridge Wells, KENT, TN3.
14) **With thanks to Dr. Siohban Leary,** Research Fellow, NMR Unit, Institute of Neurology, Queen Square, LONDON, WC1N3BG, who approached the spouses of patients involved in her research project, who agreed to act as control subjects.

Appendix G: A Copy Of The Information Sheet Given To The Control Subjects.

Multiple Sclerosis (MS) is a chronic disease of the central nervous system, affecting the brain and spinal cord. People who suffer from MS may experience a wide variety of symptoms, both physical, for example, blurred vision or weak limbs, and mental, for example, poor memory or concentration. The aim of this study is to develop a new assessment of memory function, specifically for people with MS. Such a measure is necessary because conventional memory tests, in everyday use at the moment, do not take account of the physical problems people with MS may experience. The tasks often require easy, efficient manipulation of stimuli, and fine perceptual discrimination. Thus individuals with MS, who have poor manual dexterity or visual acuity, are placed at a disadvantage, even before memory is begun to be assessed. The new test of memory function does not have these prerequisites, and more accurately reflects the abilities of people with MS. In order to identify memory problems in such individuals, it is necessary to compare their scores with the normal range, that is, the scores obtained by healthy people. To calibrate the normal range, requires healthy individuals completing the same test. The new assessment can then be used in hospitals to give a precise picture of the memory capabilities of people with MS. All details are strictly confidential and will only be used in the statistical analyses of the standardisation sample.

Appendix H: The Raw Scores Of The Control Subjects, On The Conventional Neuropsychological Tasks In The Test Battery.

Table 4.1: Cognitive Scores For The Control Group (N=85)

NART-R:	
mean (SD) number of errors	22.00 (8.16)
median (range)	22.00 (9-41)
verbal IQ mean (SD)	102.04 (9.28)
median (range)	102.00 (81-117)
performance IQ mean (SD)	103.39 (8.98)
median (range)	104.00 (81-117)
WAIS-R: vocabulary subtest	
raw score mean (SD)	44.34 (9.82)
median (range)	44.00 (21-65)
VESPAR: spatial analogy section	
raw score mean (SD)	18.64 (2.97)
median (range)	19.00 (11-25)
standard score mean (SD)	10.69 (1.11)
median (range)	11.00 (8-13)
percentile mean (SD)	63.52 (14.30)
median (range)	64.00 (25-87)

Table 4.2: Cognitive Scores For The Control Group Divided By Age

	Controls aged 18-40 years (N=38)	Controls aged 41-55 years (N=28)	Controls aged 56-70 years (N=19)
NART-R:			
mean (SD) no. of errors	24.53 (7.44)	21.86 (8.69)	18.05 (7.32)
median (range)	24.50 (9-41)	21.50 (9-41)	17.00 (9-40)
verbal IQ mean (SD)	99.34 (8.52)	102.50 (9.83)	106.74 (9.31)
median (range)	99.50 (81-117)	102.50 (81-117)	108.00 (82-117)
perf. IQ mean (SD)	100.84 (8.22)	103.75 (9.57)	107.95 (8.02)
median (range)	100.50 (83-118)	104.50 (83-118)	109.00 (84-118)
WAIS-R:			
vocabulary subtest	43.66 (8.54)	44.21 (10.26)	45.89(11.77)
raw score mean (SD)	43.50 (23-64)	40.00 (30-65)	47.00 (21-65)
VESPAR:			
spatial analogy section			
raw score mean (SD)	19.42 (2.96)	17.93 (2.88)	18.11 (2.90)
median (range)	20.00 (12-25)	18.00 (11-23)	18.00 (12-24)
stand. score mean (SD)	10.66 (1.12)	10.39 (1.07)	11.21 (1.03)
median (range)	11.00 (8-13)	10.00 (8-12)	11.00 (9-13)
percentile mean (SD)	61.74 (14.65)	62.07 (14.10)	69.21 (13.07)
median (range)	64.00 (25-86)	63.00 (27-84)	70.00 (39-87)

Appendix I: A Copy Of The Information Sheet Given To The Patients.

The aim of this study is to develop a new assessment of memory function, specifically for people with MS. Such a measure is necessary because conventional memory tests, in everyday use at the moment, do not take account of the physical problems people with MS may experience. The tasks often require easy, efficient handling of stimuli, and the ability to see fine detail. Thus individuals with MS, who have poor manual dexterity or visual acuity, are placed at a disadvantage, even before memory is begun to be assessed. The new test of memory function does not have these requirements, and more accurately reflects the abilities of people with MS. In order to understand the difficulties that some individuals with MS may have, we need to collect information from a large number of people with MS, on this test. Your decision to participate in the study will in no way affect the treatment or service that this hospital provides. You are free to discontinue your participation at any time. All details are strictly confidential and will only be used in the relevant statistical analyses.

Appendix J: The Raw Scores Of The Patient Group, On The Conventional Neuropsychological Tasks In The Test Battery.

Table 4.3: Cognitive Scores For The Patient Group

NART-R:	
mean (SD) number of errors	20.24 (10.98)
median (range)	18.50 (1-49)
verbal IQ mean (SD)	104.23 (12.44)
median (range)	106.50 (72-126)
performance IQ mean (SD)	105.46 (12.03)
median (range)	107.50 (74-127)
[1]**WAIS-R: vocabulary subtest**	
raw score mean (SD)	45.89 (11.72)
median (range)	48.00 (6-64)
[2]**VESPAR: spatial analogy section**	
raw score mean (SD)	16.66 (5.06)
median (range)	18.00 (5-25)
standard score mean (SD)	9.80 (1.99)
median (range)	10.00 (5-14)
percentile mean (SD)	54.48 (22.39)
median (range)	58.00 (7-92)

[1] data based on 99 patients i.e. 1 patient missing; [2] data based on 95 patients i.e. 5 patient missing

Table 4.4: Cognitive Scores For The Patient Group, Divided Into Short and Long Battery Subjects

	Short Battery Patients (N=50)	Long Battery Patients (N=50)
NART-R:		
mean (SD) no. of errors	18.96 (9.98)	21.52 (11.87)
median (range)	18.50 (3-42)	18.50 (1-49)
verbal IQ mean (SD)	105.62 (11.29)	102.84 (13.46)
median (range)	106.50(80-124)	106.50 (72-126)
perf. IQ mean (SD)	106.76 (10.90)	104.16 (13.04)
median (range)	107.50 (82-125)	107.50 (74-127)
[1]**WAIS-R:** **vocabulary subtest**		
raw score mean (SD)	47.10 (11.02)[1]	44.70 (12.36)
median (range)	48.00(16-64)[1]	47.00 (6-64)
[2]**VESPAR:** **spatial analogy section**		
raw score mean (SD)	17.65 (4.83)[2]	15.73 (5.13)[3]
median (range)	18.50 (6-24)[2]	16.00 (5-25)[3]
stand. score mean (SD)	10.04 (2.02)[2]	9.57 (1.96)[3]
median (range)	10.00 (5-14)[2]	10.00 (5-13)[3]
percentile mean (SD)	58.33 (23.08)[2]	50.88 (21.97)[3]
median (range)	63.50 (7-92)[2]	58.00 (7-90)[3]

[1] data based on 49 patients i.e. 1 patient missing; [2] data based on 46 patients i.e. 4 patients missing; [3] data based on 49 patients i.e. 1 patient missing

Appendix K: The Raw Scores Of The Patient Group, Who Completed A More Extensive Neuropsychological Battery.

Table 4.5: Cognitive Scores For The Patients Who Completed A larger Battery Of Neuropsychological Tests (N=50)

WAIS-R:	
digit span raw score mean (SD)	13.70 (4.40)
median (range)	12.50 (7-24)
arithmetic raw score mean (SD)	9.72 (4.37)
median (range)	9.00 (2-18)
similarities raw score mean (SD)	17.36 (5.83)
median (range)	19.00 (3-26)
[1]**VESPAR: spatial odd one section**	
raw score mean (SD)	15.82 (2.64)
median (range)	16.00 (8-21)
standard score mean (SD)	10.33 (0.94)
median (range)	10.00 (8-12)
percentile mean (SD)	59.57 (11.60)
median (range)	59.00 (25-82)
spatial series section	
raw score mean (SD)	19.49 (4.23)
median (range)	21.00 (9-25)
standard score mean (SD)	10.12 (1.89)
median (range)	11.00 (5-13)
percentile mean (SD)	56.96 (20.92)
median (range)	64.00 (3-88)

RMTW:	
raw score mean (SD)	42.54 (6.88)
median (range)	43.50 (23-50)
percentile mean (SD)	47.04 (37.50)
median (range)	50.00 (1-97)
[1]CVLT:	
standard score T1 mean (SD)	-1.47 (1.42)
median (range)	-2.00 (-4 - 3)
standard score T5 mean (SD)	-1.78 (1.97)
median (range)	-2.00 (-5 - 2)
T-score of total score mean (SD)	28.55 (17.91)
median (range)	27.00 (5-77)

[1] data based on 49 patients i.e. 1 patient missing; [2] data based on 49 patients i.e. 1 patient missing, apart from the verbal paired associates section; visual reproductions section based on 45 patients i.e. 5 patients missing