REMEDIATION EFFICACY OF THE MEMORY NOTEBOOK FOR PATIENTS WITH MEMORY DYSFUNCTION IN MULTIPLE SCLEROSIS

By

MICHELLE ANASTASIA LANGILL

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To the Faculty of Washington State University:

The members of the Committee appointed to examine the dissertation of MICHELLE ANASTASIA LANGILL find it satisfactory and recommend that it be accepted.

Chair

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Abstract

by Michelle Anastasia Langill, Ph.D.
Washington State University
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Chair: Brett Parmenter

The current paper evaluated the effectiveness of an 8-week memory notebook treatment for multiple sclerosis (MS) patients with memory dysfunction. Fourteen participants who were diagnosed with MS and had either a score indicating mild-to-moderate impairment on an objective memory test (i.e., the CVLT-II or the BVMT) *or* a self-report of a decline in memory were randomly assigned to either the Memory Notebook group (MNG) or the Supportive Psychotherapy control group (CG). Both groups received 8 training sessions for 1.5 hours over 7 weeks; on the eighth week, one hour was dedicated to training and the remaining half hour was designated to follow-up paperwork. The primary outcome measures were between-groups comparison of pre-post change on the Center for Epidemiologic Studies Depression Scale (CES-D) and the Everyday Memory Questionnaire (EMQ). In terms of secondary measures, a between-groups comparison of pre-mid-post change on the Retrospective Memory Task (5RMT) and the Prospective Memory Task (5RMT), and comparisons of pre-post change on the Functional Assessment of Multiple Sclerosis, Version 2 (FAMS-2), the State Trait Anxiety Inventory (STAI), the Epworth Sleepiness Scale (ESS), the Zung Anxiety Scale (ZAS), the Modified Fatigue Impact Scale (MFIS), and the Fatigue Severity Scale (FSS). A greater improvement of depression symptoms was seen for the MNG than the CG. Non-significant

changes were seen in clinically therapeutic directions on all other measures. This trial supports the efficacy of memory notebook training for distress reduction in MS.

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Dedication

This dissertation is dedicated to Dave.

CHAPTER ONE

INTRODUCTION

Background of Multiple Sclerosis

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system (CNS) that damages myelin in the brain, spinal cord and/or optical nerves thereby producing sensory, motor and/or cognitive impairments (Poser et al., 1983; Keegan & Noseworthy, 2002). Recent research suggests that MS can also result in axonal transection (Ferguson, Matyszak, Esiri, & Perry, 1997; Raine & Cross, 1989; Trapp et al., 1998) as well as cortical and central atrophy (Benedict et al., 2004; Simon et al., 1999; Zivadinov et al., 2001). While the cause and the early development of the disease are not fully understood, currently it is thought that MS involves an autoimmune process affecting genetically susceptible individuals, possibly triggered by environmental factors (see Thomas, Thomas, Hillier, Galvin, & Baker, 2006).

Disease Course

As defined by the National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis (Lublin & Reingold, 1996), disease course in MS is categorized as relapsing-remitting (RR), primary-progressive (PP), secondary-progressive (SP) or progressive-relapsing (PR). According to this group, RR is defined as disease relapses with full or partial recovery, with no or only minimal disease progression between relapses; PP is defined as disease progression from onset with occasional plateaus and temporary minor improvements; SP is defined as initial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaus; and PR is defined as progressive disease from onset, with clear acute relapses, with or without full recovery and continued progression between relapses.

Neurologic Impairment

The Expanded Disability Status Scale (EDSS; Kurtzke, 1983; 2007) is the most widely used system to measure neurological impairment in MS. It provides a summarized measure of a neurological examination from 0 (normal neurological exam) to 10 (death due to MS). The strengths of the scale include its widespread use allowing comparability of results, and the extensive psychometric knowledge that has been gathered. However, there are many criticisms about the scale, including its narrow range of symptom measurement and poor relationships to functional impairment (see Beatty & Goodkin, 1990) or cognitive dysfunction (Rao et al, 1991a). Another commonly used scale of physical disability is the Ambulation Index (AI; Hauser et al., 1983), which requires the patient to walk 25-feet two times as quickly as they can. The EDSS and the AI are highly correlated (r=0.96; Beatty, Goodkin, Hertsgard, & Monson, 1990).

Cost of MS

MS is a substantial public health problem. Approximately 400,000 Americans suffer from MS (National Multiple Sclerosis Society, 2004). This condition is frequently disabling, preceded only by epilepsy and stroke as neurological cause for disability (Social Security Administration Office of Disability, 2003). Such disability results in dependence upon others for mobility and activity participation in more than 50% of all MS patients (British Society of Rehabilitation Medicine, 1993). MS also produces one of the largest groups of long-term care and support service usage in people aged 65 years or younger (Prouse et al., 1991).

Such disability significantly impacts employability (see Scheinberg et al., 1981) as MS occurs primarily during peak years of employment (ages 20–50; National Multiple Sclerosis Society, 2004). Research related to employment in MS indicates that the majority of patients (>90%) have a history of working before diagnosis (Larocca, Kalb, Kendall, & Scheinberg,

1982; Larocca, Kalb, Scheinberg, & Kendall, 1985); employment reduces to approximately 60% at the time of diagnosis, and only 20–40% are employed following diagnosis (Rumrill & Roessler, 1999; Rumrill, 1996; Beatty, et al., 1995). From socioepidemiological studies, it is shown that MS leads to unemployment in 50-80% of the cases within a ten-year disease course (Kornblith, LaRocca & Baum, 1986).

Cognitive impairment is a relevant, but often overlooked contributor to disability and unemployability in MS. Caused by CNS deterioration, cognitive impairment is a common MS symptom (Foong et al., 1998; Rao, 1995; Brassington & Marsh, 1998), and affects about half of all MS patients (Arnett et al., 1997; Heaton et al., 1985; Pelosi, Geesken, Holly, Hayward, & Blumhardt, 1997; Peyser, Edwards, Poser, & Filskov, 1980; Rao et al., 1991a). The most commonly affected cognitive domains are processing speed, memory, and executive functioning (Beatty et al., 1990; Penman, 1991; Petersen & Kokmen, 1989; Rao et al., 1984). The degree of impairment in MS is typically mild to moderate (Rao et al., 1991a), although severe dementia has been observed in 20-30% of cognitively impaired MS patients (Rao, 1996). Due to the generally moderate nature of cognitive impairment in MS, such dysfunction is often undetected or misattributed as depression (Lincoln et al., 2002) or other psychological factors (Rao et al., 1991a). Studies investigating potential predictors of occurrence and severity of cognitive dysfunction have not been fruitful. Rao (2004) summarized that longitudinal studies examining the relationship between changes in cognitive impairment and disease factors such as disease duration and neurological signs have been inconsistent. For example, a 10-year follow-up by Amato et al. (2001) found that cognitive dysfunction was predicted by physical disability, disease course, and increasing age; however, such results were not found in other longitudinal studies (Kujala, Portin, & Ruutiainen, 1997; Patti et al., 1998). A more consistent finding is for

chronic progressive patients (including PP and SP) to exhibit more severe cognitive impairment than RR patients (Minden, Moes, Orav, Kaplan & Reich, 1990; Heaton, Nelson, Thompson, Burks, & Franklin, 1985; Filippi, et al., 1994). Further research is suggestive of stronger rates of cognitive dysfunction for SP than PP (Comi et al., 1995).

Associations have been established between cognitive impairment and neuroimaging showing cerebral disease, as neuropsychological defects correlate with computed tomography (CT) or magnetic resonance imaging (MRI) measures of total T2 lesion area (TLA), cerebral volume (Benedict et al., 2002; Camp et al., 1999; Rao et al., 1989; Hohol et al., 1997) corpus callosum size, (Huber et al., 1992; Rao et al., 1989, Ryan et al., 1996) and third ventricle volume or width (Huber et al., 1992; Rao et al., 1985). In terms of proton magnetic resonance spectroscopy research, Pan, Krubb, Elkins and Coyle (2001) found a correlation between both impaired memory and executive functions and lower NAA levels, a marker of axonal damage, at the periventricular white matter. Likewise, Gadea and colleagues (2004) found a relationship between right locus coeruleus axonal damage and selective attention.

Cognitive dysfunction has been linked to poor outcomes in terms of quality of life (see Mullins, 2001), including reductions in social involvement and employability (Rao et al, 1991b), negative mood (Gilchrist & Creed, 1994), sexual dysfunction (Amato, 1995) and psychopathology (Galeazzi, 2005). Such poor outcomes in MS can be related to cognitive factors independent of physical disability (Amato et al., 2001; 1995; Rao et al., 1991b). As discussed by Amato, Zipoli, and Portaccio (2006), typical measures of physical disability, including the EDSS, are poorly related to either functional outcome or cognitive disability in MS; alternatively, cognitive dysfunction in MS, in particular dysexecutive symptoms have been linked to poorer quality of life, regardless of MS-related physical symptoms (Cutajar et al.,

2000). However, the relationship between cognition and quality of life can be exacerbated by high depression and anxiety scores (Benito-Leon, Morales, & Rivera-Navarro, 2002).

Memory Dysfunction in MS

In terms of cognitive dysfunction, memory loss in MS is a substantial problem. Relative to healthy and clinical controls, MS patients commonly have memory impairments (Caine et al., 1986; Maurelli et al., 1992; Thornton & Raz, 1997) and between 40-60% of MS patients report memory dysfunction (Maurelli et al., 1992; Ron, 1986). Retrieval failures are common (Rao, et al., 1993) such that recognition is usually less impaired than recall (Beatty & Monson, 1991; Rao et al., 1991a; Swirsky-Sacchetti, 1992). These deficits are seen across verbal, visuo-spatial and figural items, with minimal improvement seen with cueing. However, global impairments involving explicit, recognition, and working memory are also seen (Thornton & Raz, 1997). Memory impairments in MS also can arise due to 'frontal dysfunctions.' These include metamemory, temporal order and cognitive flexibility tasks, and several authors attributed these deficits to damage to diencephalic and fronto-striatal circuits (Beatty et al., 1990; Beatty & Monson, 1991; Rao, Hammeke & Speech, 1987). Despite these impairments, several authors have demonstrated sparing of procedural, implicit and remote memory (Thornton & Raz, 1997; Rao et al., 1993; Beatty & Goodkin, 1990).

Background of Memory Remediation

Limited research has examined the efficacy of pharmaceutical intervention of memory impairment in this population (see Christodoulou et al., 2003). As such, psychotherapeutic interventions are being increasingly advocated. Based on evidence of preserved learning capacity for people with severe memory disturbances (e.g., Evans et al., 2000; Glisky & Schacter, 1989), cognitive remediation has become an important area of study in neurological disease. Memory

interventions have been developed with demonstrated beneficial effects in dementia, stroke and traumatic brain injury (TBI) patient groups (see Wilson, 1999). Although interest in memory rehabilitation in MS has grown recently, a comprehensive model comparable to those developed in the brain injury field remains to be fully elaborated. Furthermore, while many principles of memory rehabilitation developed from TBI are applicable in MS, differences in these neurological insults have to be considered when devising rehabilitative techniques. For example, unlike a brain injury, which can be an isolated incidence, MS is a chronic progressive disease; as such, compensation for memory deficits is important because improvement may not be possible (Berg, Koning-Haanstra, & Deelman, 1991).

As summarized by Wilson (1999) the intention of cognitive rehabilitation is to: i) manage specific deficits relating to memory impairments; ii) optimize remaining cognitive abilities, as well as physical, psychological and social functioning; iii) prevent the loss of autonomy and independence in daily living; iv) enhance self-esteem and life quality; and v) facilitate participation in preferred activities and valued social roles. Wilson also discussed principles of cognitive rehabilitation that increase efficacy of delivery, including: i) an individualized approach with personally-relevant goals; ii) inclusion of the patient, families and health care professionals during treatment planning; iii) an emphasis on improving functioning in the everyday context; and iv) an integrated, holistic approach accounting for affect, life experience and social context. As shown in TBI research, the application of these remediation principles results in more efficient uses of remaining capacities and improved emotional coping (Berg et al., 1991). Restorative approaches have been poorly supported in previous cognitive rehabilitation research (Benedict, 1989; National Institutes of Health, 1998).

A recent review by Sohlberg and Mateer (2001) investigated the efficacy of current memory intervention approaches. These authors summarized that restorative techniques like memory practice drills and mnemonic strategy training have not shown to be efficacious (Schacter & Glisky, 1986) or result in little benefit in real-life contexts (Miller, 1992). On the other hand, general cognitive remediation techniques such as prospective memory training and metamemory training have shown benefits (Sohlberg, White, Evans & Mateer, 1992a, 1992b; Hannon, 1995). Successful results have also been seen for domain specific techniques such as expanded rehearsal time/spaced retrieval (SR) methods and preserved priming (method of vanishing cues; see Sohlberg & Mateer, 2001).

One intriguing area of cognitive intervention focuses on compensatory strategy training, including the use of external aids. Research supports the reduction of everyday memory and planning problems with the use of external aids for participants with various brain disorders (Wilson et al., 2001). External memory aids are probably the most useful devices for helping memory impaired people as they are more likely to be used long-term (Wilson & Watson, 1996) and provide recognition cues that restrict the response choices (Bourgeois, 1991). Numerous external memory aids have been suggested including notebooks, calendars, signs, and clocks (Wilson & Moffat, 1984).

In a recent workshop presented at the 35th International Neuropsychological Society Meeting (2007), Mateer identified the work of Schmitter-Edgecombe, Fahy, Whelan, and Long (1995) as a seminal cognitive rehabilitation study in the area of memory notebook training. Despite the small number of participants involved in the research, this work was identified due to the quality of the intervention and appropriate assessment and outcome measures. In this study, eight participants with a TBI were randomly assigned to either a memory notebook training

group or a supportive psychotherapy group. The intervention involved sixteen sessions over eight weeks, and was described in good detail, citing behavioral learning principles (Dougherty & Radomski, 1987; Sohlberg & Mateer, 1989) and educational strategies for individualizing instruction (Callahan & Clark, 1982) to justify methodological procedures. Pre- and post-treatment outcome measures assessed objectively-measured recall and everyday memory using the Logical Memory I and II scales and the Visual Reproduction I and II scales from the Wechsler Memory Scale—Revised (Wechsler, 1987), and the profile score from the Rivermead Behavioral Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1991), respectively. Self-reported everyday memory failures were measured with the Everyday Memory Questionnaire (EMQ; Sunderland, Harris, & Baddeley, 1983) and self-perceptions of insight and mood were measured with the Global Severity Index from the Symptom Checklist 90-Revised (SCL-90-R; Derogatis, 1983). Results indicated fewer everyday memory failures after the memory notebook training but not supportive psychotherapy intervention as measured with the EMQ. However, as expected, no improvements were found for either group on the objectively-measured recall or everyday memory indicators. The effects of memory notebook training also demonstrated improved coping, insight and anxiety, as measured with the SCL-90-R. This study highlights the benefits of the memory notebook in people with memory problems due to a TBI.

Patients with a TBI are different from patients with MS in many important ways. For instance, a TBI is a specific, one-time injury whereas MS is a progressive disease resulting in decline over time. Thus, to gain a better understanding of how a memory notebook may be beneficial to patients with MS, a review of the literature examining external memory aides in patients with other types of progressive dementing illnesses is necessary. Six studies reflecting the general quality and methodology of this literature were identified. Each study varied in its

use of an actual memory notebook as compared to memory and conversation aids, as well as the severity of dementia of the participants. Unfortunately, the samples used were small as the majority of these studies had fewer than 5 participants. Indeed, a goal of this paper was to investigate the efficacy of external memory aids with a meta-analysis, but this was not possible due to the dearth of controlled studies.

In a small, preliminary study, Bourgeois (1990) found that a wallet memory aid containing autobiographical information improved quantitative and qualitative conversation factors at post-treatment through six-week follow-up for 3 moderate to severe dementia patients. In a larger follow-up to this study, Bourgeois, Dijkstra, Burgio and Allen-Burge (2001) found that a 12-page memory notebook containing autobiographical information and their daily schedule improved quantitative and qualitative conversation factors in 63 moderate to severe dementia patients, with 63 patients in the treatment condition and 62 controls within a nursing home setting. A similar study was conducted by Hoerster, Hickey, and Bourgeois (2001). These authors found that a 25-page memory notebook containing autobiographical information improved quantitative and qualitative conversation factors between four residents with dementia and their nursing assistants, although no follow-up testing or control group was employed. Another study by Johnson (1997) investigated the use of a memory notebook that was divided into three sections: i) calendar, ii) residential facility information and iii) autobiographical information with four residents diagnosed with probable Alzheimer's disease. This author found that statements made in interview about the notebook were positive, but no changes were seen on the Multidimensional Observational Scale for Elderly Subjects (MOSES; Helmes, 1988) an objective measure of behavioral problems, at post-treatment testing.

Other external memory aids have also been evaluated. In a case study by Holmes (2000), it was found that a pocket-sized notebook containing autobiographical information reduced behavioral excesses for a patient at post-treatment testing with dementia using the Revised Memory and Behavior Problems Checklist (RMBPC; Teri, 1992). Yasuda et al. (2002) investigated the use of a Sony IC Recorder as a voice output memory aid with eight moderate-severe dementia patients. For five of the eight participants, this recorder was effective in prompting to-do tasks at post-treatment testing.

Overall, these studies show tentative support for memory aids in the dementia population. To validate these findings, larger studies with random assignment and control groups are still needed.

In terms of methodology, the memory notebook technique has been modified over the years. McKerracher, Powell and Oyebode (2005) recently identified key intervention components of the memory notebook approach. These authors compared two memory notebook styles in an ABAB (intervention 1 - intervention 2 - intervention 1 - intervention 2) format with a 46-year-old male attending an outpatient brain injury rehabilitation unit. Each phase consisted of 12 to 14 days, for a total of 54 consecutive days of memory notebook training. Instead of engaging their participant in extensive neuropsychological evaluation, which measures cognitive abilities essentially unrelated to everyday memory (Wilson, 1993; Sunderland, Harris, & Baddeley, 1983), the patient was administered the RBMT (Wilson, Cockburn, & Baddeley, 1991) an ecologically valid method of investigating cognitive deficits, which may more accurately characterize targeted abilities. The authors also measured mood and anxiety, noting the adverse relationship between these factors and rehabilitation outcome identified by several authors (Fluharty & Priddy, 1993; Malec, Schafer, & Jacket, 1992).

The methods utilized by McKerracher and colleagues (2005) included the following: firstly, using Burke and colleagues' (1994) reality testing method, steps were taken to reduce the patient's resistance and highlight the impact of the patient's memory impairments on daily life. Secondly, tasks, activities, and items that the participant wanted to better recall were identified, and the memory aid was introduced. The following training principles were also implemented: 1) a "Today" bookmark, 2) a "to do" list, and 3) role-playing activities. Based on the recommendations of Donaghy and Williams (1998), a bookmark was included in the memory notebook titled "Today" with the following mnemonics: A) Cross Out (cross out the timetable task just completed); B) Notes (note what you have done in the memory log); and C) Next (check next timetable task). Additionally, the bookmark had the following reminders: A) Who (did you meet/contact); B) When (did you meet/contact them); and C) What (did you do). Based on errorless-learning principles (Baddeley & Wilson, 1994; Evans et al., 2000; Wilson, Baddeley, Evans & Shiel, 1994), these mnemonics were reviewed systematically and written on the "Today" bookmark to provide a prompt and minimize errors outside of training. The authors also included a "to-do" list as originally recommended by Sohlberg and Mateer (1989). This list consisted of a daily timetable and memory log sections that were reviewed with the patient and administrator each session. Finally, the authors noted that the patient and administrator engaged in role-playing exercises to help teach training principles, as suggested by Donaghy and Williams (1998).

McKerracher and colleagues then compared the following notebook styles: "The Standard Diary" as proposed by Sohlberg and Mateer (1989) and "The Modified Diary" from Donaghy and Williams (1998). The essential difference between the notebooks were that The Standard Diary contained a weekly timetable and a separate "to do" list and The Modified Diary

contained a daily timetable and a "to do" list on adjacent pages. To measure the efficacy of the different diary styles, the authors utilized a technique proposed by Donaghy and Williams (1998) involving the completion of five prospective memory tasks (5PMT). These tasks were described as client-relevant, verifiable by the administrator and examined to ensure equality in task complexity across sessions. The authors found that The Modified Diary was preferable, in that 4-5 of the 5PMTs were completed each week, compared to only one of the 5PMTs ever completed with The Standard Diary. This difference was attributed to the visibility of the to-do list every day due to the adjacent page set-up in The Modified Diary, whereas in The Standard Diary the to-do list was difficult to find, and therefore the tasks were not completed. They recommended The Modified Diary as the preferred system to compensate prospective memory and retrieval processes.

Remediation of Memory Dysfunction in MS

A handful of studies have empirically examined the remediation of memory impairment in patients with MS, with mixed results. Most of these studies examined the efficacy of restorative or general cognitive remediation techniques, with a handful of these studies mentioning the use of an external aid. Only one study primarily investigated the utility of an external aid, specifically the memory notebook. These studies are discussed below.

In a non-randomized prospective between-group design, Chiaravalloti and DeLuca (2002) investigated the effectiveness of the Generation Effect as a cognitive technique to improve new learning in MS patients. Thirty-one patients with MS and seventeen healthy controls (HC) participated in the study. The MS patients were compared to 15 matched healthy controls (HC) on a neuropsychological battery. The authors characterized the MS participants as "fairly high functioning" and only found poorer performance on a measure of working memory

and processing speed (i.e., the Paced Auditory Serial Addition Test; PASAT) for MS patients as compared to HC. Depressed mood, as measured with the Beck Depression Inventory (BDI; Beck et al., 1961), and anxiety, as measured with the State Trait Anxiety Inventory (STAI; Spielberger, 1983), were significantly greater for the MS patients than the HC group. The intervention, administered to both the MS and the HC groups, was based on the Multhaup and Balota (1997) Generation Effect protocol, emphasizing the principles of cognitive science. The standard protocol involved asking participants to both read complete sentences and generate sentences endings, and then having them recall the sentences. Multhaup and Balota modified this procedure to optimize the sensitivity of the items, by using a recognition task rather than a recall task, and adjusting the list length, distractor items, and number of test items, to accommodate cognitively impaired individuals. Training consisted of 12 weekly, one-hour sessions.

The study compared cognitive performance between the HC and MS groups at immediate, thirty-minute and 1-week follow-up time points. The authors concluded that the Generation Effect protocol was an effective means to maximize learning in both MS and control participants. While this small study is supportive of this protocol in "fairly high functioning" MS patients, the results do not tell us how this restorative technique could benefit patients with more significant cognitive impairment.

Chiaravalloti, DeLuca, Moore and Ricker (2005) investigated another restorative cognitive technique in a randomized prospective double-blind between-group design. Specifically, they investigated the effectiveness of the Story Recall Technique (SRT) to improve memory in MS outpatients with learning deficits. Twenty-eight MS outpatients with impaired verbal learning across the mild, moderate and severe ranges participated in the study; fourteen were randomly assigned to the control group (CG). Verbal learning was assessed using an

adaptation of the Buschke Selective Reminding Test (DeLuca, Barbieri-Berger & Johnson, 1994; DeLuca, Gaudino, Diamond, Christodoulou & Engel, 1998).

The intervention, administered only to the experimental group, was referred to as the Story Memory Technique protocol, and based on the work of Goldstein and colleagues (1988). This intervention involved a computer-assisted program based on a mnemonic strategy devised to rehabilitate cognitive brain injuries specifically focusing on list learning. This strategy included the Ridiculously Imaged Story (RIS) technique, wherein participants are taught to invent a story to help them learn a list. The control group was administered memory exercises consisting of imagery and context-use training. Baseline neuropsychological testing was followed by eight twice-weekly 45-minute training sessions for four weeks followed by an immediate follow-up at week six and a long term follow-up at week 11.

As measured with total learning score change on the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001), the SRT group did not show improved memory and learning, depressed mood or anxiety compared to the control group at either follow-up points. Interestingly, upon post-hoc analysis, benefits of the intervention were seen on the HVLT-R for the moderate-to-severely impaired patients with little improvement seen for the mildly impaired patients. In addition, improvement of everyday memory as measured by the Memory Functioning Questionnaire (MFQ; Gilewski, Zelinski & Schaie, 1990) was observed for the experimental group as compared to controls at both follow-up points. This small study is supportive of the Story Memory Technique for improving self-reported memory for MS patients and for improving memory and learning for MS patients with more severely impaired verbal learning.

The utility of computer assisted interventions has been examined by other researchers. In a randomized prospective double-blind between-group design, Tesar, Bandion and Baumhackl (2005) also demonstrated the effectiveness of computer-assisted neurological training program for MS outpatients. This program focused on restorative and general cognitive remediation techniques. Twenty MS patients with "mild to moderate cognitive impairments," as determined by a neuropsychological battery were randomly assigned into two groups. Mood was measured with the BDI (with study exclusion for scoring above the mild range), and fatigue was measured with the modified Fatigue Impact Scale (MFIS; Kos et al., 2006). A follow-up questionnaire regarding perceived treatment benefits was also administered. One patient dropped-out, leaving ten participants in the neurological training group (NTG) and nine in the control group (CG).

Treatment for the NTG consisted of twelve 90-minute sessions, in addition to regular rehabilitation care (e.g., physical therapy, occupational therapy, etc.). The CG followed rehabilitation care as usual. Post-testing measurements were at four weeks (end of intervention) and at a three-month follow up. The RehaCom (Schuhfried, 2001) cognitive retraining program, a memory and attention retraining software package with a specialized keyboard to limit the impact of motor impairments, was used as the intervention. This intervention targeted "the two cognitive areas most severely affected" based on the work of Gauggel, Konrad and Wietasch (1998). While both groups demonstrated gains, consistent with a practice effect, the primary endpoint of greater improved scores for the NTG as compared to the CG at immediate and follow-up was found for several cognitive measures (a card sorting test and spatial-constructional test) but not for the secondary endpoints of fatigue and mood. This small study is supportive of the efficacy of RehaCom for remediation of cognitive factors in MS patients.

Although the above studies support the use of a computer-assisted restorative/general cognitive remediation techniques in patients with MS, the results of a randomized prospective double-blind between-group study by Solari, Mancuso, Motta, Mendozzi, and Serrati (2004) are more equivocal. This study included 82 MS outpatients at six Italian centers. The participants were randomly assigned into two groups. After seven patients dropped-out, forty participants remained in the memory training group (MTG) and thirty-seven remained in the control group (CG). Cognitive impairment was defined as scoring below 80^{th} percentile on at least two components of the Brief Repeatable Battery of Neuropsychological Tests (BRBNT; Rao, 1990) and self-reported poor attention or memory. Mood was measured with the Chicago Mood Depression Inventory (CMDI; Nyenhuis et al., 1995; Chang et al., 2003). Assessment of health-related quality of life was assessed with the MS Quality of Life- 54 scale (MSQOL-54; Vickery, Hays, Harooni, Myers, & Dixon, 1995). All MTG and CG participants were treated on an individual basis as outpatients for 45 minutes, twice a week, for 8 consecutive weeks. The MTG training program involved the previously described RehaCom (Schuhfried, 2001) training package. The control treatment consisted of simplified RehaCom visuo-constructional and visuo-motor coordination retraining procedures as a sham intervention. The assessments took place at baseline, at 8 weeks (the end of intervention) and at a 16 week follow-up.

The a priori defined primary endpoint was an increase of 20% or more in at least two BRBNT test scores at 8 weeks compared to baseline. This endpoint was found for approximately half of both the MTG and CG patients at both the 8-week and 16-week time points. These authors also found that patients with lower test scores at baseline generally demonstrated greater gains on BRNBT subtests. Secondary efficacy endpoints on the CMDI and MSQOL-54 indicated a slight improvement in mood at 16 weeks for both groups and an improvement in quality of life

for both groups seen at both 8 and 16 weeks. The authors did not analyze the statistical significance of within-group changes. The authors concluded that this study does not support the efficacy of computer-assisted retraining interventions specific to memory and attention in MS. However, it is quite possible that the sham intervention was as helpful a measure at providing cognitive rehabilitation as the treatment intervention as gains were noted in both groups across cognitive, mood and quality of life measures. Also, the authors indicated that the groups differed at baseline, such that the MTG participants were older, had lower scores on the word list generation test, and a higher score on the 10/36 spatial recall (delayed recall) test. In sum, this moderate-sized study is tentatively not supportive of the efficacy of RehaCom for remediation of cognitive or emotional factors in MS patients, although the strong sham intervention may have masked treatment effects.

In a case study, Allen, Longmore and Goldstein (1995) evaluated a 47-year old employed man with 12 years of education on a computer-assisted cognitive remediation intervention. Full Scale IQ was 95, according to the Wechsler Adult Intelligence Scale- Revised (WAIS-R; Wechsler, 1981). The participant self-reported cognitive problems. A ten-point difference was found between the WAIS-R Full Scale IQ and the Wechsler Memory Scale- Revised (WMS-R; Wechsler, 1987). The Memory Quotient was interpreted as a mild to moderate impairment in memory. Symptoms of anxiety and depression were measured using the Beck Anxiety Inventory (BAI; Beck & Steer, 1990) and the BDI, respectively. The participant began taking interferon-β 1b two weeks before pre-testing and was maintained on a similar dose throughout training and follow-up. The intervention involved the earlier-described ridiculously imaged story (RIS) technique, in addition to the face-name method wherein participants learned to associate names

with an acquaintance or a celebrity name (see Goldstein et al., 1988). Training consisted of 15 sessions, plus a one session follow-up after 30 days.

Results indicated that the training resulted in improved list-learning, but not face-learning, abilities. In addition, the authors observed that the participant learned the strategies efficiently. Several subtests used to measure generalization of the learning [the Logical Memory subtest from the WMS-R, the California Verbal Learning Test (CVLT; Delis et al., 1987), the Buschke Selective Reminding Task (BSRT; Buschke, 1973) and alternate versions of the training tasks] demonstrated improvements. However, the authors did not address the possibility of practice effects. No changes were observed on the BAI. Scores on the BDI indicated a decline in depression during treatment sessions, but a strong *increase* at one month follow-up compared to pretest due to "personal factors." This case study is supportive of intact learning ability for one patient with MS and the efficacy of list-related but not name-related mnemonic strategy for this participant.

In a follow-up to their case study, Allen, Goldstein, Heyman and Rondinelli (1998) began with ten MS patients in their study, with eight completing training. To measure the presence of cognitive impairment the WMS-R and the RBMT were administered. Self-reported everyday memory was measured utilizing the Memory Questionnaire (MQ; Sunderland, Harris, & Baddeley, 1983) and mood was measured with the BDI. The intervention was described as a similar list/story and face/name computer-assisted learning procedure as reported earlier by Allen, Longmore and Goldstein (1995). Training consisted of 15 sessions, each lasting 30 minutes, two or three times a week; no follow-up session was reported.

Likely because of high level performance from the beginning, improvement on the training tasks (e.g., list and face learning tasks) was not found. Although a trend toward

improvements on self-reported memory failure was noted, only an improvement of depressed mood was found, wherein scores improved from the mild-moderate range to the minimal range. The authors compared the results with a study examining similar restorative cognitive training in patients with head injuries (Sunderland, Harris & Gleave, 1984), and concluded that MS participants learned the strategies more quickly and achieved better story recall than head-injured participants. They also suggested that since the MS participants learned so efficiently, they might only require 1-2 sessions of training. Anecdotal comments by participants indicated that their ability to apply these memory skills to real-life situations contributed to a significant reduction in depressed mood. This study lends support for the efficacy of computer-assisted mnemonic strategy for emotional, although not cognitive, factors in MS patients.

Another study also failed to find benefits of restorative/general cognitive remediation techniques. In a non-randomized prospective between-group design, Chiaravalloti, Demaree, and Gaudino (2003) investigated the Repetition Effect in MS patients. Sixty-four MS outpatients were compared to twenty matched healthy controls (HC) on a neuropsychological battery. The intervention, administered to both the MS patients and HC group, was based on a Selective Reminding Test protocol (Buschke & Fuld, 1974). Using a modified version of the Buschke Selective Reminding Test, participants learned a list of 10 words over a maximum of 15 trials, training to a pre-specified criterion. The authors demonstrated that by providing more learning trials for MS patients with cognitive difficulty, the patients improved their learning and memory performance on the instrument. Number of words recalled were then compared between the HC and MS groups immediately after the intervention, and then after 30-minutes, 90-minutes and 1 week. The authors reported a trend for the MS patients who required more learning trials to perform worse on the learning trials, concluding that "individuals with MS may not benefit from

repetition in isolation, but rather require the use of more intensive rehabilitation strategies" (pg. 58) when encoding information. In sum, this moderate-sized study is not supportive of the Repetition Effect in MS patients.

Unlike previously mentioned studies, a study by Lincoln and colleagues (2002) included both restorative/general cognitive remediation techniques and compensatory techniques. Two hundred and twenty three outpatients with MS participated in the study. Eighty two patients were randomly assigned to the control group (group A), 79 to the assessment group (group B) and 79 to the intervention group (group C). Participants in Group B and Group C received a three hour cognitive assessment, including the BRBNT and the Guys Neurological Disability Scale (GNDS), and various quality of life (QOL) measures. During the data analysis phase, the patients were classified by presence of cognitive dysfunction, as defined by the BRBNT or the GNDS. Patients in Group C additionally received a non-referenced cognitive rehabilitation program for identified deficits, which included compensatory techniques, such as external aids, as well as restorative/general techniques, such as mnemonics. The non-intervention groups did not complete any form of pseudo-intervention. The three groups were compared on the outcome measures at four and eight months.

Significant differences were found on questions assessing overall quality of life on the MSQOL- 54 at eight, but not at four, months. Patients in the control group (A) rated their quality of life and life satisfaction significantly higher in comparison with patients in the assessment group (B), but not the treatment group (C). The authors concluded that no intervention benefit was observed, but recommended including a measure of client satisfaction when these kinds of interventions are used. This large-scale study is not supportive of the efficacy of remediation

using a mix of restorative/general and compensatory techniques for cognitive or emotional factors in MS patients.

Another similar type of treatment study also failed to find improvements in cognitive functioning, but did report improvements in emotional functioning. In a randomized prospective single-blind between-group design, Jonsson, Korfitzen, Heltberg, Ravnborg and Byskov-Ottosen (1993) investigated the effectiveness of "cognitive training and neuropsychotherapy" for cognitive impairment in MS patients. Forty MS inpatients participated in the study; 20 were randomly assigned to the experimental group and the remaining 20 were assigned to the control group (CG). The authors did not specify the manner in which they estimated "mild to moderate cognitive dysfunction".

The intervention was administered only to the experimental group and included goal-directed treatment based on the patient's individual neuropsychological profile, including compensation activities (e.g., visualization techniques, memory aids), direct cognitive training based on researched principles of cognitive remediation (Prigatano, 1986; Wilson, 1987; Meier, Benton & Diller, 1987), and "neuropsychotherapy" for improved coping and acceptance for MS-related impairment. In contrast, the control group was administered non-specific mental stimulation including: discussing literature and arts, playing games, and disease acceptance. Intervention consisted of 60- to 90-minute training sessions three times per week for an unknown number of weeks, with an average of 17.2 training hours. Participants were assessed at approximately 45-days after the intervention and again at six months.

Improved scores on a visual-spatial perception measure were found for the experimental group at the 45-day follow-up, but this was not maintained at the six month follow-up. Participants in the experimental group also reported improved depression, but not anxiety, at

both follow-up points. The authors concluded that life quality measures but not cognitive measures are the best instruments to measure neuropsychological treatment effects. Finally, these authors offered that the "best outcome is obtained when the patient during treatment learns insight and compensatory techniques, assimilated and used in daily living" (pg. 399). This small study is supportive of the efficacy of remediation using a mix of restorative/general and compensatory cognitive remediation techniques for emotional, but not cognitive, factors in MS patients.

Another type of intervention was evaluated by Benedict and colleagues (2000). Rather than examining the effectiveness of specific cognitive remediation techniques, they investigated the utility of neuropsychological counseling on emotional and behavioral changes in cognitively impaired patients with MS. Fifteen outpatients with MS participated in this randomized, single-blind treatment outcome study; eight were randomly assigned to the Neuropsychological Compensatory Training Group (NCT) and seven were randomly assigned to the Non-Specific Supportive Psychotherapy Group (NSP). The MS patients were characterized as "cognitively impaired" compared to 15 matched healthy controls (HC) on a neuropsychological battery. Mood was measured with the BDI; however participants who met DSM-IV diagnostic criteria for depression were excluded. Assessment of personality as reported by an informant caretaker was measured with the Hogan Empathy Scale (HES; Hogan, 1969) and the revised NEO Personality Inventory (NEO-PI; Costa & McCrae, 1992). Aggression, also as reported by a caretaker, was measured using a brain-injury scale (Linn, Allen, & Willer, 1994).

The NCT intervention was based on a non-referenced program emphasizing the principles of cognitive-behavioral therapy, including education, awareness training, and social skills training. The NSP control group offered non-specific supportive psychotherapy. Control

participants were not included in the intervention. Training consisted of 12 weekly, one-hour sessions and a two-week follow-up. As expected, the aggressive behavior was reduced in the NCT group but not the NSP group. Neither group showed improvements in mood, although this may have been due to excluding depressed patients. This small study is supportive of the use of NCT to reduce aggressive behavior in MS patients with cognitive impairment

The aforementioned studies have emphasized restorative/general cognitive rehabilitation techniques in patients with MS. While a handful of these studies mentioned adding a compensatory strategy to the rehabilitation techniques, only one study primarily focused on the utility of such a strategy in this population. In a randomized prospective single-blind between-group design, Mendoza, Pittenger and Weinstein (2001) investigated the effectiveness of an external memory aid, specifically the memory notebook, in MS patients. Twenty MS inpatients participated in the study; ten were randomly assigned to the Memory Notebook Group (MNG) and ten were randomly assigned to the control group (CG). While the control group was significantly older than the memory notebook group, the authors justified the age difference as the result of ensuring an equal gender ratio between groups.

All participants underwent a screening battery while the memory notebook group was administered an extended test battery. Mood was measured with the BDI. The intervention was administered only to the experimental group, and included a non-referenced memory notebook training protocol in which certified nursing assistants problem-solved memory-notebook related issues with the patient everyday for ten weeks. The control group was offered care as usual. Post-testing only occurred at the end of the ten weeks. Staff was trained in 5 one-hour sessions, on various treatment-related topics.

The primary endpoint of improvement on the originally administered cognitive measures was not found. The secondary endpoint of improvement on the BDI was found for the memory notebook group but not the control group. The authors remarked that "the observed effects [may have] resulted from changes in the staff's tolerance for the patients symptoms" (pg.13). This small study is supportive of the efficacy of a memory notebook technique for emotional but not cognitive factors in MS patients, although this effect may have been mediated by staff interaction factors.

Recommendations for Future Studies

In reviewing these eleven cognitive remediation outcome studies in MS, the efficacy of cognitive rehabilitation in MS is inconclusive. Most of the studies focused on restorative/general cognitive mediation techniques and found that some benefit may be derived from the RehaCom procedure, mnemonic strategies, Story Memory Technique, or Generation Effect, although more rigorous assessment, replication as well as longitudinal assessment are needed. The Repetition Effect was not recommended for this population. The remediation of emotional and quality of life factors, on the other hand, was supported in many studies, with any combination of applied cognitive, compensatory and therapeutic techniques. These may be mediated by non-specific therapeutic treatment effects, which warrant continued careful examination. For these studies replication as well as longitudinal assessment is needed. Furthermore, in reviewing this literature, additional factors relating to participants and interventions were identified to help future research in this area become more rigorous.

In terms of participant factors, the first issue is the determination of the presence of clinically definite MS. Diagnosing MS can be a lengthy process, often requiring other neurological, medical and psychiatric etiologies to be ruled-out first. Due to this issue, it can be

helpful to report both the duration since symptom onset and the time since diagnosis, as these variables often differ. To ensure the validity of the MS diagnosis, only patients with definite MS, using referenced criteria (e.g., McDonald et al., 2001; Polman et al., 2005; Poser et al., 1983; Schumacher, 1965) should be included in these studies. Since differential cognitive outcomes are related to types of MS (e.g., PP, RR, SP) inclusion of this information is informative. Finally, to further describe MS, inclusion of some measure of physical functioning/disability, such as the EDSS or AI, is recommended. In the previously described studies, it was noted that many of the participants were diagnosed at least ten years prior to the study, as mean years since diagnosis was 11.2 (SD = 6.8), reported in four studies. Mean years since symptom onset was substantially longer at 22.2 (SD = 9.8).

Only seven studies reported the specific criteria used to diagnosis MS. Six of the studies referenced Poser et al., whereas one study referenced Schumacher. Seven studies reported MS types in terms of PP, SP and RR. The average ratio of MS types was 1PP: 4 SP: 4 RR. No studies reported any participants with PR, although this may be due to the rarity of this type. Finally, using the EDSS (nine studies) or the AI (two studies) physical symptoms due to MS were rated as 4.8 (SD = 2.2) and 3.5 (SD = 2.6), respectively, demonstrating mild to moderate physical impairment for most participants. Unfortunately, many of these factors were not addressed in all studies, thereby limiting our understanding of the samples cited.

In regards to the presence of cognitive impairment for participants, two issues should be clearly defined. Firstly, in order to ensure that the participants are in fact impaired, minimum standards of cognitive impairment should be defined a priori using referenced criteria. These standards can involve scoring below a cut point using objective measures, self-report measures, or both. Typically, such cut points are performance of at least 1.5 standard deviations below

published test norms or compared to control participants. Secondly, the maximum standards of cognitive impairment using referenced criteria should be defined with the purpose of preventing participants with severe dementia from participating in the study. Often, this involves a cut-off score on an objective measure [e.g., Mini Mental Status Exam (MMSE); Dementia Rating Scale (DRS); Cognitive Capacity Screening Examination (CCSE), Kaufman Short Neuropsychological Procedure (K-SNAP)]. The severity of the cognitive impairment for participants (e.g., mild, moderate, severe) should be characterized to inform readers of the participants' ability, and utilizing both performance and self-report measures of cognition should be considered, as these may provide unique cognitive characterizations. Justifying the use of the cognitive measures is important and authors should cite the validity of these measures in the assessment of MS patients.

With regard to the aforementioned studies, assessment was generally conducted in an extensive manner across studies. Pre-morbid IQ was assessed in eight studies, all using some type of vocabulary subtest, either from the WAIS-R (three studies), the Wide Range Achievement Test-3 (WRAT-3; one study) and German equivalent (Multiple Vocabulary Test-B; MWT-B; one study), or a version of the National Adult Reading Test (NART; three studies). WAIS-R subtests were utilized to assess verbal abilities in eight studies. Language was measured only in three studies, using the Boston Naming Test (BNT). Visual-spatial measures were included only in three studies; two of these using WAIS-R subtests, and the other using the Judgment of Line Orientation (JLO) and the Complex Figure Test (CFT). WMS-R subtests were used to assess memory abilities in four studies. List-learning measures were used in six studies, including the CVLT (two studies) and the HVLT (two studies). Four studies included visual memory measures, such as the Brief Visual Memory Test-Revised (BVMT-R; one study) and the

10-36 (one study). Other memory measures were incorporated in four studies, including for example, the BSRT (two studies) and the Recognition Memory Test (RMT; one study). In terms of executive functioning measures, seven of the studies included instruments measuring attention and processing speed, typically the PASAT (six studies), in addition to the Trail Making Test (TMT; four studies) and the Symbol Digit Modalities Test (SDMT; two studies). Higher level executive functioning skills were measured with a card sort in five studies, with two studies specifically using the Wisconsin Card Sorting Test (WCST); and five studies using the Stroop Test. Although most studies included a large number of assessment instruments in their protocols, most were incomplete as they did not include one from each important assessment area (general intelligence, language, visual-spatial ability, memory, attention/processing speed, and executive abilities). Therefore, the studies provide an incomplete understanding of the full range of cognitive deficits experienced by the participants in their intervention studies.

The collection of a plethora of participant variables is useful in defining the functionality and living circumstances of the MS patient population. These include age, education, estimated pre-morbid intelligence, living situation (e.g., inpatient or outpatient), the degree and range of depression [e.g., BDI, CMDI, General Health Questionnaire (GHQ-28)], anxiety (e.g., STAI), functional impairment [e.g., Extended Activities of Daily Living (EADL); GNDS], quality of life [e.g., MOS 36-Item Short-Form Health Survey (SF-36); MSQOL-54] and fatigue (e.g., FIS). Again, it is recommended that whenever possible, the use of these measures should be justified with the validity of these measures in the assessment of MS patients cited. With regard to the reviewed studies, the participants were often middle aged as the average participant's age was 45.3 years (SD = 9.9), as reported in all eleven studies; most participants had at least some college as the average years of education was 14.3 years (SD = 2.3), reported in seven studies;

average estimated pre-morbid IQ was in the average range (M = 103.8, SD = 8.7), reported in four studies. Eight of the studies enrolled outpatients (a total of 464), and two of the studies enrolled inpatients (a total of 60). Only two of the studies reported about the employment status of their participants.

Subjective measures for emotion and coping- related issues were included in the eleven studies, although the specific measures used varied substantially. A measure of depression was present in ten of the studies (typically the BDI), whereas anxiety measures (BAI, STAI) and everyday memory measures were present in four and three of the studies, respectively. Everyday performance measures (RMBT; Test of Everyday Attention (TEA), Robertson, Ward, Ridgeway, & Nimmo-Smith, 1994)) and quality of life measures (SF-36; MSQOL-54) were each included in two of the eleven studies. Measures for personality, aggression, functional impairment, and fatigue were each only included once in the eleven studies. Although several of the studies recommended utilizing subjective measures as primary outcome indicators for outcome studies, only a handful actually included them.

Another important consideration in cognitive rehabilitation research in this population is the inclusion at least one control group composed of individuals with MS. If a pseudo-treatment is utilized then it should be ensured that it indeed has no therapeutic effect, to avoid masking a real treatment effect. A secondary control group with healthy controls could be included to compare the performance of MS patients to matched individuals without MS. If a control group is engaging in modified cognitive remediation or supportive intervention, then including an additional wait-list control group to examine "placebo" effects should be considered. Most of the reviewed research studies included a control group; indeed, nine of the studies included

prospective between-group designs, whereas only one was a case study, and one was a prospective single-group design.

To avoid group differences, control and experimental groups should be matched on the following variables: age, education, premorbid IQ (using referenced criteria; e.g., NART, WRAT-3 reading subtest, WAIS-R vocabulary subtest), male/female ratio, disease duration (either symptom duration or time since diagnosis), physical disability scores (as earlier defined), neuropsychological assessment scores and intervention hours, employment status, living situation (inpatient or outpatient), type of MS (PP, SP, RR, PR), and memory impairment severity.

Many factors can interact with the cognitive and emotional status of an individual with MS. To reduce confounds, the following exclusionary criteria could be considered: a history of other neurological disease, including TBI; a history of drug/alcohol abuse/dependence; a diagnosis of non-MS related psychiatric disorders; MS relapse/corticosteroid treatment initiation during or within one month of the start of the study; over the age of 65 years to avoid confounds of normal aging; sensory/upper limb physical disability interfering with intervention participation; and maintaining constant dosages and schedules of psychotropic drugs or drugs for spasticity, tremor, bladder disturbances and fatigue. Additionally, it is imperative for researchers to provide the number and reasons for participant drop-outs across treatment and control groups to determine if patients who stay in treatment differ from those who do not. In the reviewed studies, participant drop-out rates were noted in nine of the studies, with an average of five drop-outs per study. However, reasons for drop-outs were only listed in six of those studies.

Across studies, many important rule-outs were not applied. The most commonly applied exclusionary criteria were having a history of neurological disease other than MS (seven studies),

non-MS related psychiatric disorders (eight studies), a history of substance abuse or dependence (six studies), and MS exacerbation or initiation of corticosteroid treatment within one month prior to the study start (six studies). However, studies less often screened for participants who were older than 60 years of age (five studies), or severe visual impairment or severe motor dysfunction of the arms or hands interfering with treatment procedures (one study). Also only three studies reported excluding the data of participants who experienced an MS exacerbation during the study, and only four studies attempted to hold the participants' dosages and schedules of medications constant throughout the study. Since not one study accounted for all of these important conditions, extraneous factors may have played a role in treatment outcomes in any study.

In terms of the intervention, several recommendations have emerged, including reporting whether participants were randomly assigned to groups, describing the methods for assuring blindedness to groups, justifying the format of the intervention, including the intervention schedule, and reporting how the facilitators of the interventions were trained.

It is recommended that researchers report the method of randomizing of participants, and describe the method for assuring blindness, if the study design is either single or double blind. Ideally, a way to test the effectiveness of the blindness should be included. Regarding the reviewed studies, seven reported randomly assigning participants to treatment or experimental groups; only three of the studies were double blind and four studies were single blind. This suggests that the work is potentially contaminated with expectancy effects and selection factors. Unfortunately, blindness across both the participants and the researchers can be difficult with these types of interventions. Researchers should also report and justify whether the intervention followed an individual or group format, and whether it included a close relative or friend and

describe the role of this individual. An individualized format involving a significant other can often increase outcome efficacy. Of the 11 studies, all involved individual formats. The addition of a significant other was present in only two studies.

It would be helpful for all intervention studies to report and justify the intervention schedule in terms of hours/days/sessions/weeks, reporting the total number and the averages of these variable; the location of intervention (e.g., inpatient/outpatient) and the degree of supervision (e.g., % hours directly supervised by trained facilitator vs. individual work). Increased training hours, with greater direct supervision will likely lead to greater treatment efficacy, although the minimum standard providing the greatest benefit is very valuable outcome information. The total number of sessions in the studies averaged 17 (as reported in nine of the studies), with a range 1-70 sessions. Seven studies reported the length of sessions, which averaged one hour. Nine studies reported the number of sessions per week, which averaged 2, ranging from 1-7. The average treatment hours, a useful intervention parameter to allow quick comparison among studies, was only reported by one study (at 17.2 hours). Long-term follow-up was reported in eight studies, at an average of eleven weeks. Finally, reporting the training protocol of facilitators in terms of procedures and hours would be helpful to ensure that standards of care can be met. Only two of the studies reported the training of the research assistants; therefore, it is difficult to know the degree to which these interventions were properly administered.

In terms of the intervention procedure, it is recommended that the specific treatment protocols be clearly defined for the experimental and control groups. This includes citing and describing the theoretically and research-based principles of the treatment program and specifically discussing the stages of treatment in a manualized-like format. It would also be

helpful for each study to report the prospectively defined endpoint, including primary and secondary outcomes (e.g., cognitive, depression, anxiety, functional ability, quality of life, and/or fatigue measures) along with follow-up points, ideally at six months and one year. For the reviewed studies, the intervention formats varied from computerized mnemonic techniques (three studies), computerized cognitive skill rehabilitation training program (two studies), cognitive science effect investigations (two studies), memory notebook (one study) and neuropsychological counseling (one study). While most of the studies were described in adequate detail to convey the intervention methodology, two (Lincoln et al.; 2002; Jonsson et al., 1993) failed to describe their intervention in much detail, although both groups reported a similar mélange of intervention techniques; however, unlike Lincoln and others, Jonsson and colleagues found at least one treatment effect. Of all the eleven studies, Lincoln and colleagues (2002) did not continually facilitate their interventions with a research assistant, which may have contributed to poor treatment outcome for this study.

In summary, no particular variable was identified as of key importance in the methodological characterization of these cognitive remediation research articles for MS patients. Instead, methodological and intervention vigilance factors outweighed specific variables in relating to treatment efficacy. These variables are listed in Tables 1 through 12. In reviewing these studies, relative to other factors, a strong focus on cognitive assessment was generally observed. However, one of the primary concerns that emerged is the general lack of detail about the intervention procedures and the poor attention given to the intervention delivery.

Based on this review, it is clear that additional studies examining cognitive remediation techniques in patients with MS are needed. While most of the aforementioned studies have emphasized restorative/general cognitive remediation techniques or a combination of

restorative/general and compensatory techniques, only one (Mendoza et al., 2001) focused on a compensatory measure, the memory notebook. This is surprising considering the benefits of this technique in patients with various brain disorders (i.e., Bourgeois, Dijkstra, Burgio, Allen-Burge, 2001; Sandler & Harris, 1992; Schmitter-Edgecombe et al., 1995; Squires, Humkin & Parkin, 1997).

Hypotheses

The current study intends to improve on the existing literature in the following ways:

1. Use best practices as seen in other studies, in terms of defining and describing disease characteristics, cognitive impairment (presence and severity), participant variables, exclusionary criteria, prospective endpoints and data analyses (see Appendix A for further details).
2. Use a demographically- and disease-matched randomly-assigned control group who engage in a program of treatment equivalent in time, therapist-intervention efforts, and participant engagement (i.e., a supportive psychotherapy group) but no expected therapeutic effect.
3. Focus the remediative intervention on one strategy type. Namely, use a memory notebook program that is research-based, systematic and described in detail.

Because the Mendoza et al. (2001) study only examined the use of this technique on inpatients with moderate to severe memory dysfunction, the following study is designed to investigate its utility on outpatients with mild to moderate memory problems. Based on theoretically- and empirically-based research principles, it is hypothesized that: (a) participants in the memory notebook training group will report improved self-reported everyday memory (as measured by the EMQ) compared to those in the control group; (b) participants in the memory

notebook training group will be able to complete more prospective or retrospective memory tasks (as measured by the 5PMT) than those in the control group; (c) an improvement in mood, anxiety, health-related quality of life, and fatigue will be seen for participants in the memory notebook training group, but not in the control group.

CHAPTER TWO

RESEARCH DESIGN AND METHODOLOGY

Participants

Between May 2007 and December 2007, this study enrolled 20 people with clinically definite MS (McDonald et al., 2001). Participants were recruited from within a larger research initiative in Dr. Brett Parmenter's research lab at Washington State University (WSU). Out of 57 potential participants eight were unavailable for contact and eight did not meet exclusionary criteria due to: dementia diagnosis, dual role conflict for the provider, MDD diagnosis with ECT treatment, re-diagnosed as not MS, and three participants did not report and/or had no memory problems indicated at assessment.

Within those participants who were available to participate, twelve declined to participate in the outcome study due to: not interested (3), not a good time of the year (3), too far to travel (2), does not like groups (1), too busy (1) and family illness (1).

Nine patients agreed to participate but cancelled before pre-test due to: illness (4), too far to travel (2), too busy (2), and re-diagnosed as not MS (1). Six patients (three from each group) who had agreed to participate in the group study and underwent the pre-test, but dropped out of study on the day of the first intervention session due to: illness (2), too expensive to travel (1), too far away (1), "no longer able" (1), and did not return phone calls (1). One participant dropped out after the first intervention session due to family illness. Participation rates varied from 5 to 7 of the eight sessions offered with an average 6.42 days (0.67 SD). Absences were due to MS-related fatigue, family or work commitments, bad weather conditions, and/or doctor appointments.

Participants were excluded for any one of the following: age less than 18 years, age over 65 years, education of less than eight years, diagnosis of a non-MS related psychiatric disorders including dementia, MS symptom exacerbation or treatment with steroids within one month prior to or at any point during enrollment, or sensory/ upper limb physical disability interfering with intervention participation. Medication regimens were requested to be held constant for the duration of the study period whenever possible. No participant reported medication changes during the study period. Furthermore, participants were excluded from data analysis if they had a diagnosis of dementia in the moderate-severe or severe ranges or showed like evidence on neuropsychological testing.

Written informed consent was obtained from all patients. Protocol approval was obtained from the Institutional Review Board at WSU.

Initial Assessment

Participants were recruited from an ongoing research study wherein they were administered a three-hour neuropsychological test battery (see Table 15 for a summary of assessment measures). The battery included the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS; Benedict et al., 2002), in addition to several supplementary measures of cognition and self-report instruments (the Multiple Sclerosis Functional Composite (MSFCM; Fischer et al., 1999), the North American Adult Reading Test (NAART; Blair & Spreen; 1989), the Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977), and the Fatigue Severity Scale (FSS; Krupp et al., 1989).

Because the patients recruited for the current study were selected on the basis of reported memory complaints, they were expected to demonstrate some impairments on

neuropsychological testing; however, patients exhibiting severe memory problems (less than the 2nd percentile based on test norms on immediate and delayed recall and delayed recognition on both measures of memory) and/or severe cognitive decline (less than the 2nd percentile based on test norms on at least three measures from the MACFIMS), were to be excluded from the study, although no participants fell into this category. The neuropsychological assessment occurred on average 64 (SD = 38.99 days) days before the first treatment session.

Interested participants were screened over the telephone to determine eligibility for the study. Because the focus of the study was on either subjective or objective problems of everyday memory, the inclusionary criterion for the study was *either*: 1) a score indicating mild-to-moderate impairment on an objective memory test (i.e., the CVLT-II or the BVMT) *or* 2) a self-report of a decline in memory.

Once eligibility was determined, the second assessment was scheduled. Participants were asked to bring to the initial assessment a list of their medications, their calendar, their phone book, pictures of family, and a snack; this served as the 5PMT measure. The second assessment session entailed the administration of the following instruments: the Rivermead Behavioral Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1991); the EMQ (Sunderland, Harris & Baddeley, 1983), Functional Assessment of Multiple Sclerosis, Version 2 (FAMS-2; Cella et al., 1996) and the State-Trait Anxiety Inventory (STAI; Spielberger, 1983). In addition to the 5PMT, during this administration session participants were asked to rate their confidence about five recent life events (5RMT). In order to measure environmental demands, including home, work or school, and extracurricular settings, a semi-structured interview was administered (see Appendix B). The second assessment occurred on average 22.08 (11.41 SD) days before the first treatment session.

Group Assignment

Participants provided written informed consent and then were assigned randomly to the Memory Notebook Group (MNG) or the Control Group (CG). Those conducting the neuropsychological evaluations were blind to group membership, and participants were not aware of the treatment received by the other group.

Groups did not differ with regard to the following variables: age, sex, education, premorbid IQ, neuropsychological functioning, intervention hours or disease severity as estimated by the Ambulation Index or the Multiple Sclerosis Functional Composite (see Table 13). However, a difference in the groups approached significance on the FAMS-2 ($t10$ =2.21 p = 0.05), such that the MNG group reported more functional impairment (M = 48.8, SD = 33.38) than the CG (M = 96.83, SD = 41.75). No differences were found for any of the following variables: type of MS, employment status, living situation (inpatient or outpatient), months since symptom onset, or months since diagnosis.

Groups were also matched by MS disease modifying pharmaceutical treatments, including interferon beta (IFN; Avonex, Rebif), glatiramer acetate (Copaxone), natalizumab (Tysabri) and no-treatment conditions (see Table 14). This is due to variation in disease severity, disease management, and side-effects associated with each treatment. For example, IFN may have differential effects on mood and cognition compared to other MS disease modifying treatments or no treatment conditions. Studies are mixed as whether IFN is associated with depression. One study found a side-effect rate of 20% (Jacobs et al., 2000), whereas other studies did not find an increased rate with this treatment (Patten & Metz, 2001; 2002). However, some evidence indicated that IFN treatment resulted in better scores on neuropsychological instruments (Fischer et al., 2000; Pliskin et al., 1996).

Intervention

Training principles applied to the Memory Notebook Group (MNG) intervention were based primarily on the summary of theoretically- and empirically-based research principles discussed by McKerracher, Powell and Oyebode (2005). These authors presented several training components relevant to the introduction of the diary and the diary format. First, measures were taken to reduce the patient's resistance and highlight the impact of the memory impairments, as outlined by Burke and colleagues, (1994; see Fluharty & Priddy, 1993). As described by these authors, the main component of "reality testing" entails casually asking the client about a topic of interest or giving the client a prospective memory task within the session, and then asking the participant to recall the topic or prospective memory task. Participants with everyday memory problems will typically have rapid forgetting of these details, and this type of "reality testing" can increase the participant's awareness and help to demonstrate the utility of the instrument. Second, the administrator introduced a standardized memory aid that was personalized to meet the participant's needs. This phase involved identifying tasks, activities and items that the client would like to incorporate into the notebook. Third, training principles (as outlined below) were explained followed by role-playing exercises to integrate the principles into use, as recommended by Donaghy and Williams (1998).

As originally identified by Sohlberg and Mateer (1989), training of the memory notebook involved a three stage approach: (1) acquisition (how to use it), (2) application (where and when to use it), and (3) adaptation (how to update it). To avoid a lengthy and frustrating acquisition phase, the Donaghy and Williams (1998) recommended diary set-up was employed: a) two facing pages for each day of the week containing: i) a column with a daily timetable; ii) a column

with a to-do list; and iii) a memory log; and b) a marker indicating "Today" (see Appendix E and F).

As originally recommended by Sohlberg and Mateer (1989), each section was reviewed with the patients each session. The following two mnemonics were taught to the patient: CONN and WWW. CONN refers to: 1) Cross Out (cross out the timetable task just completed); 2) Notes (note what you have done in the memory log); and 3) Next (check next timetable task). WWW refers to: 1) Who (did you meet/contact); 2) When (did you meet/contact them); and 3) What (did you do). Based on errorless-learning principles (Baddeley & Wilson, 1994; Evans et al., 2000; Wilson, Baddeley, Evans & Shiel, 1994), these mnemonics were reviewed systematically and written on the "Today" marker to provide a prompt and minimize errors outside of training.

To avoid allowing the participant to repeat and thereby strengthen erroneous use of the memory notebook, the Donaghy and Williams (1998) role play exercises were employed, such as asking the participant to engage in various tasks, while covering the earlier-discussed procedures. These authors ultimately recommended only allowing the participant to take the memory notebook home after he or she has demonstrated procedural learning for the mnemonic devices, how to cancel a scheduled activity and add an event/to-do item. The participants in this study were able to master these role-playing procedures during the first session.

During the weekdays of the first two weeks of training, a total of 10 daily phone calls were made to increase compliance (as per Schmitter-Edgecombe et al., 1995). During the daily phone calls a standardized questionnaire was administered, which varied based on group membership (see Appendix C and D).

All participants in the memory notebook training group were treated within small groups varying from 1-4 participants as outpatients for 90 minutes, once a week, for eight weeks. A

measure of prospective memory and a measure of retrospective memory was administered on three occasions: at baseline testing, at session five of the intervention, and at the final session of the intervention. To measure prospective memory, participants were asked to bring in five items (5PMT): a list of their medications, their wall calendar, their phone book, at least one picture of a family member, and a snack. Total number of items remembered was recorded. To measure retrospective memory, participants were asked to complete five memory tasks (5RMT): Which to-do type items did you complete last Wednesday? How many appointments did you have last Tuesday? Do you have any medical appointments next week? Did you reschedule any of your appointments last Monday? Did you visit with relatives last weekend? These items were paired with questions of confidence about their answer on a scale of 0-100% confidence (i.e., metamemory assessment). The assessment of everyday memory complaints (the EMQ) and psychological functioning (the CES-D, the STAI, the FAMS-2, and the FSS) occurred at baseline and at the end of intervention on the 8th week.

The therapist administering the Memory Notebook intervention was a graduate student in a clinical psychology doctoral program that was supervised by a licensed clinical psychologist. Training in the Memory Notebook intervention entailed: reading many articles about memory notebook training, reviewing the research standards for the study, and participating as a training therapist. The training entailed previous experience observing the intervention for several sessions before applying intervention principles under the supervision of a lead therapist for several sessions. Trained research assistants at the undergraduate level or above were responsible for assisting with setting up appointments, administering the battery of tests, conducting the daily phone calls, and scoring and entering data.

Measures

Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS; Benedict et al., 2002): The MACFIMS is a brief neuropsychological battery designed to identify cognitive dysfunction in patients with MS. The following measures were included in this battery: word fluency (COWAT), visual-spatial perception (JLO), verbal learning (CVLT-II), visuospatial learning (BVMT-R), sustained attention and processing speed (PASAT; SDMT), and executive function (the D-KEFS Sorting Test).

The Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1989) is a test of semantic retrieval and word fluency. Participants were provided three letters of the alphabet (C, F, and L) and were instructed to say as many words as they could that begin with that letter in 60-seconds. Proper names or the same word with different endings (e.g., boy, boys) were not counted. The examiner recorded all responses. The dependent variable on the COWAT is the total number of correct responses across all three trials with no maximum.

The Judgment of Line Orientation Test (JLO; Benton, Sivan, Hamsher, Varney, & Spreen, 1994) is a measure of visual-spatial perception. It requires participants to identify an angle defined by two stimulus lines from among those defined by a visual array of eleven lines covering 180 degrees. The dependent variable on the JLO is the total number of correct responses with a maximum of 30.

California Verbal Learning Test, 2nd Ed. (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000): The CVLT-II is a test of verbal memory and conceptual ability. The test consists of 16 words belonging to one of four categories. Participants were orally presented with a list of words and then asked to repeat the words in any order. This continued for five trials. After the five trials, another list of words was presented and again, participants were asked to repeat as many

words as they could remember. The participants were then asked to freely recall as many words as they could remember from the first list ("free recall"), then to recall words from the first list according to a specific category ("cued recall"). At this point, there was a break of at least 20-minutes, after which the participants were again asked to recall the first list, first in the free recall format, then in the cued recall format. Finally, participants were presented with a recognition portion of the test, with 44 words read aloud. Participants indicated if the word was or was not part of the initial learning trials. The following variables were derived from the CVLT-II: total words from trial 1, trial 5, total immediate recall, and delayed recall. A score was also calculated based on total words recalled from trials 1, 2, 3, 4, and 5.

The Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997; Benedict, Schretlen, Gronigen, Dobraski, & Shpritz, 1996) assesses visuospatial learning and delayed recall. Participants were presented with a learning matrix of six simple abstract designs that they were allowed to study for ten seconds. After the ten seconds, they were instructed to draw the designs from memory as accurately as possible and in the correct location on the page. Participants had three trials to learn the designs, and then after a delay of approximately 25 minutes, the participants were asked to create the designs for a delayed recall trial, again as accurately as possible and in the correct location. After this a recognition trial was administered, in which participants were asked to respond "yes" or "no" to 12 items. The following variables were derived from the BVMT-R: total of design accuracy and location from trial 1, trial 3, total immediate recall, and delayed recall.

The Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) is a measure of sustained attention and information processing speed. Participants were instructed to listen to a series of single digit numbers that were presented via a tape recorder at the rate of one every

three seconds. Participants listened to the first two digits, added them together, and told the examiner the answer. When the next number was presented, participants were asked to add it to the digit directly preceding it and again report the answer to the examiner. There were 61 numbers for the participants to listen to and add. After the first portion of the test, participants were given a second trial with the digits presented at a quicker pace, one every two seconds. Again, 61 numbers were presented. Each portion of the test has a maximum of 60 correct answers. The following variables were derived from the PASAT: total correct from trial 1 and trial 2.

The Symbol Digit Modalities Test (SDMT; Smith, 1982) is a measure of processing speed and working memory. In the SDMT, the participant was presented with a series of nine symbols, each of which is paired with a single digit in a key at the top of a sheet. The remainder of the page has rows of symbols that the subject paired with the digit associated with each of these as quickly as possible. This is a measure of processing speed and requires visual scanning and, to a lesser extent, secondary memory as participants must either rapidly locate the correct pairing on the key or recall these symbol-digit pairings. Only the oral version of the SDMT was administered to minimize confounds due to upper extremity weakness or incoordination. The administrator recorded the items as the participant called them out. The dependent variable on the SDMT is the total number of items correct in ninety seconds.

The D-KEFS Sorting Test (DST; Delis, Kaplan & Kramer, 2001) is a measure of executive functions, specifically of conceptual reasoning that permits the differentiation of concept formation from conceptual flexibility. In the "free sort" condition, participants were presented with six shapes and instructed to sort them into two groups with three cards in each group, verbally identifying both of the groups on each sorting trial. The participants were asked

to continue categorization of the groups in this manner for both of the two card sets until they were unable to generate new sorts. Subsequently, the participants were administered the "cued sort" condition, wherein the administrator arranged the shapes into two groups of three shapes and asked the participant to identify each group, for both sets of shapes. Dependent variables include number of correct sorts, description (evaluating the quality of the description of the sorts), and number of repeated sorts.

The North American Adult Reading Test (NAART; Blair & Spreen, 1989) is a measure of premorbid cognitive function. For this instrument, the participants were asked to read a list of 64 words that cannot be properly pronounced by sight; the words must be retrieved from memory for correct pronunciation. The dependent variable on the NAART was the total number of incorrect responses, which was then used in an equation to predict Full Scale IQ.

The Multiple Sclerosis Functional Composite Measure (MSFCM, Fischer et al., 1999): The MSFCM is a brief neurologic assessment battery that is comprised of quantitative functional measures of three key clinical dimensions of MS. These include: leg function/ ambulation (Timed 25-Foot Walk), arm/hand function (9-Hole Peg Test), and cognitive function (PASAT 3.0). The PASAT is already included in the present study as a measure of the MACFIMS (see above). Scores on component measures are converted to standard scores (z-scores), which are averaged to form a single MSFC score.

The Timed 25-Foot Walk (T25W; Schwid et al., 1997): is a quantitative measure of leg function and ambulation. The participants were asked to walk 25-feet as quickly as possible without losing their balance or falling. The task was immediately re-administered by having the patient walk the same distance back to the starting point. Assistive devices were used when

applicable. The dependent variable is the amount of time (in seconds) that it takes the patient to walk 25 feet, averaged over the two trials.

The 9-Hole Peg Test (9-HPT; Mathiowetz, Weber, Kashman, & Volland, 1985; Goodkin, Hertsgaard & Seminary, 1988): is a quantitative measure of upper extremity motor speed and coordination. The participants were told to pick up and insert pegs one at a time into each of nine holes laid out in a square pattern, and then to remove these pegs one at a time. Both the dominant and non-dominant hands were tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand). The dependent variable is the amount of time (in seconds) that it took the patient to insert and remove all nine pegs for each hand averaged over the two trials.

The Ambulation Index (AI; Hauser et al., 1983): is a measure of physical disability based on the Timed 25-Foot Walk. The AI is a semi-quantitative instrument which incorporates ambulation-related disability (timed walking) into an ordinal scale from 0 (normal status) and 9 (wheelchair-bound and unable to transfer independently).

The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989): The FSS is a self-administered scale consisting of nine items that address the severity of participants' fatigue. Participants were instructed to rate each item on a scale from 1 (strongly disagree) to 7 (strongly agree) according to how strongly they agree with the item. The ratings were totaled, with greater scores indicating greater experiences of fatigue.

The State Trait Anxiety Inventory (STAI; Spielberger, 1983): The STAI is a self-report measure of anxiety, consisting of 20 items measuring "State Anxiety," and on the reverse side of the page, 20 items measuring "Trait Anxiety." Participants were asked to rate each item on a scale from one (not at all) to four (very much so), with reference to how they feel "*right* now,

that is, *at this moment*" for the first 20 items (State Anxiety) and how they "*generally* feel" for the last 20 items (Trait Anxiety). The ratings were reverse-scored as appropriate, and summed, with higher scores reflecting greater experiences of anxiety.

The Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977): The CES-D is a self-report measure of depression. This scale consists of 20 items pertaining to four features of depression: depressed affect, positive affect, somatic and retarded activity, and interpersonal issues. Participants were asked to rate each item on a scale from 0 (rarely or none of the time) to 3 (most or all of the time) with reference to how they felt during the past week. The ratings were summed to yield a total score, with higher scores reflecting a greater level of depression.

The Rivermead Behavioral Memory Test (RBMT; Wilson, Cockburn, & Baddeley, 1991): The RBMT is an analogue measure of everyday memory situations consisting of several subtests. These subtests include: Name, Belonging, Appointment, Story-Immediate and Story-Delayed subtests. The Name subtest involved remembering the name of a person presented in a photograph after a short delay of approximately 20 minutes. The Belonging subtest is a measure of prospective memory in which participants were asked to remember to ask for an object of theirs that was taken from them earlier. They also were asked to state the location of the object. The Appointment subtest is also a prospective memory test; the participants were instructed to ask a certain question ("When are you going to call me about the test results?") when a buzzer set for 20 minutes rings. The Picture and Faces subtests are both measures of visual recognition memory. In the Picture subtest participants were instructed to name the line drawings of ten common objects, which were shown one at a time for five seconds each. After a filled delay of about ten minutes, the participants were asked identify the pictures from among 20 cards, which

were presented individually. In the Faces subtest five pictures of faces were shown one at a time for five seconds each. Participants identified the five faces from among 10 cards after a filled delay of about ten minutes. The Story subtest involves memory for a brief prose passage tested in a free recall format immediately after presentation (Story-Immediate) and at a 30-minute delay (Story-Delayed). The Orientation and Date subtest entails 10 such questions. The subtests requiring participants to walk around the testing room according to a specific route, picking up and delivering messages (Route Immediate, Messages Immediate, respectively) and recall the route and messaged at a 30-minute delay (Route Delayed and Messages Delayed), was substituted for all participants due to foreseeable mobility impairment, with model versions of the tasks utilized (Model Route Immediate, Newspaper Immediate, Model Route Delayed and Newspaper Delayed; Clare, Wilson, Emslie, Tate & Watson, 2000). A composite score (RBMT-TOTAL) was calculated as the sum of the "Standardized Profile Score" (SPS) for each subtest. The SPS was developed to equate the subtests, allow for comparisons between subtests, and provide a total score. It ranges from 0 to 2.

The Everyday Memory Questionnaire (EMQ; Sunderland, Harris & Baddeley, 1983): is a quality of life measure developed for MS patients. This scale consists of 28 items. A recent review (Cornish, 2000) identified five underlying factors: Retrieval, Task Monitoring, Conversational Monitoring, Spatial Memory and Memory for Activities. Participants were asked to rate each item on 9-point scale from 1 (not at all in the last six months) to 9 (more than once a day).a scale from 0 (not at all) to 4 (very much) with reference to how they felt during the past week. The ratings were summed to yield a total score, with higher scores reflecting more memory difficulties.

The Functional Assessment of Multiple Sclerosis, Version 2 (FAMS-2; Cella et al., 1996): is a quality of life measure developed for MS patients. This scale consists of 59 items (44 scored items) divided into six subscales: mobility, emotional well-being (depression), general contentment, thinking/fatigue, and family/social well-being. Participants were asked to rate each item on a scale from 0 (not at all) to 4 (very much) with reference to how they felt during the past week. The ratings were summed to yield a total score, with higher scores reflecting a better quality of life.

Primary and Secondary Outcome Measures

To limit the number of comparisons, it was decided a priori to conduct a between-groups comparison of pre-post change on the EMQ (total score) and the CES-D (total score) as primary outcome measures. These outcome measures were selected due to improvements found by memory notebook studies on such measures in TBI populations (Schmitter-Edgecombe, et al., 1995), dementia (Bourgeois, Dijkstra, Burgio & Allen-Burge, 2001) and MS populations (Mendoza et al., 2001). In addition, as discussed above, self-reported memory problems (e.g., Chiaravalotti et al., 2005) and depressive symptoms (e.g., Allen et al., 1995; Allen et al., 1998; Chiaravalotti et al., 2002; Jonsson et al, 1993; Solari et al., 2004) frequently improved with other types of cognitive remediation in MS populations.

In terms of secondary measures, a between-groups comparison of pre-mid-post change on the Retrospective Memory Task (5RMT) and the Prospective Memory Task (5PMT) was conducted, with total number of recalled items and average feeling of confidence of recalled items as the dependent variable. Between-group comparisons of pre-post change on the FAMS-2 (Total Score), STAI (State and Trait Total Scores), and FSS (Total Score) were also chosen as

secondary outcome measures. Cognitive measures were not re-administered, as no change was expected (Jonsson et al., 1993; Quemada et al., 2003; Schmitter-Edgecombe, et al., 1995; Wilson et al., 2001; Wright et al., 2001).

CHAPTER THREE

RESULTS

Statistical analyses

It was calculated that a trial with 85% power and a level of significance of 5% (one-tailed) required 8-10 patients per group to detect the difference between the memory notebook intervention, and control intervention.

Due to the study's small sample size, analyses were chosen to reduce the risk of Type I and Type II errors. Separate 2 x 2, or 2 x 3 repeated measure analysis of variance (ANOVA) on a fixed factor of Group (MNG and CG) and repeated measure of Time (Pre- Post, or Pre-Mid-Post) was performed on the primary and secondary outcome measures. For measures violating the heterogeneity of the variance assumption, the Friedman test, a non-parametric repeated measures ANOVA was administered, and for post-hoc exploration, the Wilcoxon signed-rank non-parametric test of simple effects was administered.

Primary Outcome Measures

The repeated measures ANOVA of self-reported everyday memory failures for the MS participants as measured with the EMQ revealed a trend [F (1,9) = 3.62, p = 0.09], but no interaction with Group [F (1,9) = 1.29, p = 0.28], as shown in Figure 1. This indicated that there was a trend for MS participants receiving either the Memory Notebook training or supportive

psychotherapy to report an improvement in self-reported everyday memory failures. Of note, although not statistically significant, the improvement in EMQ mean scores for MNG group was four times greater than that of the CG group. As an exploratory analysis, to potentially reduce the variance on the EMQ, instead of using the total score, the total number of items endorsed (i.e., scores greater than zero) was tallied and compared across groups and time points. The repeated measures ANOVA of the EMQ tally revealed no main effect [F (1,10) = 1.58, p = 0.24] nor an interaction with Group [F (1,10) = 2.93, p = 0.12], as shown in Figure 2.

To evaluate the effect of treatment upon mood, the CES-D was examined. The heterogeneity of the variance was problematic for the pretest CES-D values. Upon examining the data, outliers were equivalent on either side of the mean; therefore these data were analyzed with the Friedman test, a non-parametric repeated measures ANOVA. The procedure involves ranking each difference score, and then considering the values of ranks by columns. The mean pre-rank score of 3.10 and the mean post-rank score of 8.42 approached significance (Z = -1.560, p = 0.06 one-tailed), indicating that the change was more substantial for patients who reduced their endorsement of depression over the course of treatment. Therefore, as shown in Figure 3, this test revealed a main effect for the CES-D from pre-treatment to post treatment.

To investigate the interaction of group over time on the CES-D, a Wilcoxon signed-rank test was administered, which is a non-parametric simple effects test. Using this procedure, it was revealed that the mean for the MNG was greater at the pre-treatment (M = 25.00; SD = 16.77) as compared to the post-treatment (M = 8.83; SD = 8.16) conditions (Z = -1.99; p = .046). This result is indicating a decline in depression symptoms with the MNT. In contrast, with the CG the means were similar across the pre-treatment (M = 15.83; SD = 10.53) and post-treatment (M = 16.17; SD = 7.78) conditions (Z = -.687; p = .492). Furthermore the means were the same

between the MNG and the CG at pre-treatment (Z = -.946; p = .344) and post-treatment (Z = -.734; p = .463). Generally, these results can be interpreted as a change in depression scores for the MNT but not the CG on the CES-D.

Secondary Outcome Measures

The repeated measures ANOVA for the prospective memory task revealed a main effect [$F(1,9) = 5.31$, p = 0.03], but no interaction with Group [$F(1,9) = 0.08$, p = 0.92]. As can be seen in Figure 4, post hoc analysis revealed that all participants in the study, regardless of the group, were equally able to remember to complete more prospective memory tasks at mid-treatment (M = 4.58) and post-treatment (M = 4.42), than at pre-treatment [M = 2.67; all t's(11) >2.6, $p < .05$]. Mid- and post-treatment means did not significantly differ ($p > 0.05$).

Likewise, the repeated measures ANOVA for the retrospective memory task revealed a main effect [$F(1,9) = 4.62$, $p = 0.04$], but no interaction with Group [$F(1,9) = 1.63$, p = 0.25]. As can be seen in Figure 5, post hoc analysis revealed that all participants in the study, regardless of the group, on a scale of 0-100, felt more confident about their ability to remember their activities at post-treatment (M = 94.67) than at pre-treatment [M = 85.43; $t(11)$ 2.6, p = .02]. Pre- and post-treatment means did not significantly differ from mid-treatment (M = 94.12; $p > 0.05$).

Using repeated measures ANOVAs, no significant differences between the notebook training group and the supportive therapy group were found for the anxiety, fatigue, or MS symptom indicators ($p > 0.05$).

CHAPTER FOUR

DISCUSSION

This time-limited, outpatient treatment-outcome study presents preliminary data that suggest that MS patients can benefit from the use of an external memory aid. After eight weeks of 1.5 hour weekly sessions, the participants in the memory notebook groups experienced a more significant decline in self-reported depression than the participants in the supportive psychotherapy control group.

Depression is common in MS with prevalence estimates ranging between 23%-54% (Joffe, Lippert, Gray, Sawa, & Hovarth, 1987; Sadovnick, et al., 1996; Patten, Metz, & Reimer, 2000; Schiffer, Caine, Bamford & Levy, 1983; Minden, Orav, & Reich, 1987). Depression in MS may affect treatment adherence (Mohr et al., 1997), and/or quality of life (Wang, Reimer, Matz, & Patten, 2000; Benito-Leon, Morales, & Rivera-Navarro, 2002; Fruehwald, Loeffler-Staska, Eher, Saletu & Baumhackl, 2001), and is related to disease severity (Patten, Lavorato, & Metz, 2005) and markers of disease activity (Mohr, Goodkin, Islar, Hauser, & Genain, 2001). The measure of depressive symptoms in this study was the CES-D, which using the cut-off score of 16 or greater, is 75% predictive for a diagnosable depressive disorder for the MS population (Pandya, Patten, & Metz, 2005) although the negative predictive value is as yet unknown.

Several studies have observed a decrease in depressed mood symptom subsequent to memory remediation interventions in MS (Allen, Longmore & Goldstein, 1995; Allen et al., 1998; Jonsson et al., 1993; Mendoza, Pittenger & Weinstein, 2001). This study supports earlier results of Mendoza et al. (2001) who found statistically and clinically significant improvements in the depression of patients in the notebook group as compared to the control group. In the

Mendoza study, the authors observed that increased interaction and positive attention from nursing staff may have accounted for some of the effect. The current study attempted to reduce this by having the same therapist interact with both groups in a qualitative and quantitatively similar manner.

Based on the reduction of depressive symptoms seen in the current study and other memory remediation interventions with MS participants (Allen, et al., 1995; Allen et al., 1998; Jonsson et al., 1993; Mendoza et al., 2001) perhaps these interventions should be viewed from a distress-reduction model, such that the memory notebook is a tool that enables an increased ability to overcome one's memory deficits may lead to a reduction in distress for the individual. This concept is characterized by the Locus of Control (LOC; Rotter, 1966) model, a generalized belief regarding the degree to which outcomes are controlled by an individual's actions (internal control) or by external forces (external control). A great body of research links internal LOC to depressive symptomatology. A meta-analysis of 97 studies found that greater externality was associated with greater depression, with a mean effect size of $r = .31$ (Benassi, Dufour & Sweeney, 1988) with the CES-D measure of depression and the Levenson (1973) measure of LOC producing the strongest effects for adults. These authors concluded that depressed individuals tend to view outcomes as beyond personal control, in agreement with theories proposed by Bibring (1953) and Seligman (1975). In a cross-section study of 60 MS outpatients, internal locus of control was negatively related to depression (Halligan & Reznikoff, 1985). In addition, an internal LOC is associated with a high level of generalized self-efficacy (Judge, Erez, Bono, & Thoresen, 2002) and better adjustment to chronic illness (Strickland, 1978).

Everyday Memory Failures

The improvement in EMQ mean scores for MNG group was four times greater than that of the CG groups, although the resulting EMQ interaction was not statistically significant. This may be due to the low power resulting from our small sample size and the large variance in responses. Recruitment occurred over a period of six months, and despite a high refusal rate, the target of 20 participants was met, although six participants dropped out before the first session. Refusal was often due to financial, family or work commitments. Difficulties with recruiting for remediation intervention research within the MS population has been previously reported (i.e., Jonsson et al., 1993; Lincoln et al., 2002; Solari, 2004). However, based on feedback requested at treatment termination, a clinical effect occurred for the treatment group that was not present for the supportive psychotherapy group. While members from both groups reported beneficial effects from participation, the memory notebook group made comments specifically about improvements in information management and increased confidence about their memory problems (see Appendix I). Perhaps participants who have mild-moderate memory dysfunction, like those in this study, use a broader frame of reference when considering everyday memory failures than participants with moderate-to-severe memory dysfunction. Unlike participants with moderate-to-severe memory dysfunction, who may depend almost entirely upon the notebook for memory of daily events, participants with mild-to-moderate memory dysfunction can participate in and recall the daily interactions for which the notebook cannot always compensate. This may include conversations, interactions and procedures in the community, at home or at work when one is away form the notebook. Therefore, the EMQ may not be the most efficient tool for tracking changes in notebook use. Instead, for participants with mild-to-moderate memory dysfunction, perhaps the best way to track change is to measure concepts that directly improve with the notebook (see Appendix H).

Prospective and Retrospective Memory Tasks

In examining the Prospective Memory Task, it was observed that participants from both groups remembered to bring the five items at the mid- and post-treatment assessment points compared to pre-treatment, regardless of the presence of the memory notebook to record the information. Perhaps these participants with mild-to-moderate memory problems were able to learn the items, since the items on the prospective task did not change at mid- and post-treatment follow-up. Moreover, some participants used a strategy to overcome their memory problems, such that they carried the five items with them at all times.

In examining the Retrospective Memory Task, confidence in their ability to remember completing specific tasks increased for participants from both groups from pre-treatment to post-treatment, again regardless of the presence of the memory notebook to record the information. As with the Prospective Memory Task, the items on the retrospective task did not change. Thus, these participants with mild-to-moderate memory problems were able to learn the items, regardless of the availability of a notebook. Also, their confidence may have increased simply as a function of participation in multiple assessment points. This is especially possible since there was no objective measurement of whether the items they recalled completing had actually been completed, for either group.

Anxiety, Functionality and MS Symptomology

No significant improvements were found for either the MNG or the CG group for the anxiety, fatigue, or MS symptom indicators. However, though non-statistically significant, means for each of these measures changed in a therapeutically indicated direction for the notebook training group as compared to the supportive therapy group. Again, the lack of

statistical significance may be due to the low power resulting from our small sample size and the large variance in responses.

Limitations

One limiting factor for the findings of this study is that the participants in this group are highly self-selected. As described earlier, the final participants were the 12 willing out of a pool of 57 potential participants. Non-participants described barriers of finance, illness severity, travel conditions and family commitments in addition to a preference for individual treatment. These types of difficulties are similar to those experienced by patients who did participate. However, among participants there was a high rate of absence from treatment. While this rate did not differ between groups, 2 to 3 participants in each group missed three sessions. Therefore the impact of the full 8-week treatment program may have been diluted due to participant absences. Another limiting factor was the group setting. Although some participants commented that they appreciated the increased social support and opportunity to interact with other people with MS several patients from rural areas did not join the treatment due to concerns of potentially revealing their MS to coworkers in a group setting, and others stated that they were not comfortable in a group-therapy setting. Therefore, these results are limited to those with the means and the interest to participate in group research, and are limited by less-than-ideal participation rates for those enrolled.

In terms of treatment compliance, participants had varying levels of interest in using the notebook, which also varied in the amount of details entered into the notebook. In particular, one participant felt that the notebook had limited value and wrote in it infrequently, and another participant valued the use of the notebook, but had a difficult time with writing in details. In the

latter case, the difficulty may have been due to executive dysfunction. Participants also commented that some days they were too fatigued to write in their notebooks.

Future Directions

Overall, the research suggests that a relatively simple treatment implemented with minimal formal training improved the mood of these high-functioning MS patients with memory dysfunction. Future studies should consider the following:

- working with participants with less functionality and greater memory impairment
- examining the role of caregivers in implementing and maintaining a notebook system
- developing an assessment instrument for measuring changes in everyday memory that, in contrast to the current instrument, the EMQ, might be more easily impacted by the notebook training (see Appendix H)
- examining the influence of medical variables common in the MS population (i.e., influence of co-occurring neurological deficits, medications, fatigue, and sensory deficits) on successful use of the memory notebook. In particular, fluctuations in MS symptoms may mask treatment effects. Perhaps one means to overcome this is increase the assessment points to measure if improvement is occurring on average over time
- investigating the maintenance of memory notebook skills patients with MS and memory dysfunction at six month, one year and longer longitudinal follow-up points.
- assessing the amount of intervention and reinforcement in the form of booster sessions or feedback needed to maintain use of the memory notebook, and the maintenance of improved mood.

- creating alternate versions of the prospective and retrospective memory tasks for improved follow-up measurement.

Furthermore, steps can be taken to enhance remediative treatment for persons with MS. In particular, due to the numerous boundaries to treatment described above, often related to disease fluctuation and difficulty with travel, individualized, in-home care could be offered.

Of note, all participants in the present study were functioning within the average to high average range of intelligence, and had at least twelve years of education. Therefore the results of these studies are limited in scope to participants within this demographic. Future research may evaluate the efficacy of the memory notebook on a lower functioning, less educated sample. Nonetheless, the current study demonstrates that the memory notebook training program for MS patients with memory dysfunction has greater efficacy for reducing depression symptoms compared to non-specific supportive psychotherapy.

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Table 1. Overview of participants in reviewed cognitive remediation studies in multiple sclerosis.

	Total N	N in treatment group	N in other group	N in control group	Outpts	Inpts	Employ. status
Allen 1995	1	1 MS	x	X	1	0	Yes
Allen 1998	8	8 MS	x	X	?	?	?
Benedict 2000	30	8 MS	7 MS	15 HC	15	0	?
Chiaravalloti 2002	46	31 MS	x	15 HC	31	0	?
Chiaravalloti 2005	28	14 MS	x	14 MS	28	0	?
Chiaravalloti 2003	84	64 MS	x	20 HC	64	0	?
Jonsson 1993	40	20 MS	x	20 MS	0	40	?
Lincoln 2002	237	79 MS	79 MS	79 MS	223	0	?
Mendoza 2001	20	10 MS	x	10 MS	0	20	?
Solari 2004	77	40 MS	x	37 MS	82	0	?
Tesar 2005	19	10 MS	x	9 MS	20	0	50%
Sum	*571*	*285*	*86*	*219*	*464*	*60*	*2R: 9NR*
Average	*54*	*11*	*2*	*9*	*8*	*2*	
Avg. w/o Lincoln	*35*						

Table 2. Overview of delivery in reviewed cognitive remediation studies in multiple sclerosis.

	Study Type	Site	Random	Blind
Allen 1995	Case Study	Pittsburgh	X	x
Allen 1998	PSingleG	Pittsburgh	X	x
Benedict 2000	PBetweenG	Buffalo	Yes	Single
Chiaravalloti 2002	PBG	New Jersey	X	?
Chiaravalloti 2005	PBG	New Jersey	Yes	Double
Chiaravalloti 2003	PBG	New Jersey	X	?
Jonsson 1993	PBG	Denmark	Yes	Single
Lincoln 2002	PBG	UK	Yes	Single
Mendoza 2001	PBG	Boston	Yes	Single
Solari 2004	PBG	Italy	Yes	Double
Tesar 2005	PBG	Austria	Yes	Double

Sum	*1C:9BG:1CG*	*7 US: 4 EU*	*7R: 4NR*	*4S:3D:2?:2X*

Table 3. Overview of demographics in reviewed cognitive remediation studies in multiple sclerosis.

	Group	AGE years	SD	Education years	SD	IQ est.	SD
Allen 1995	TX	47	x	12			
Allen 1998	TX	36.6	8.71	14	2.45	95.36	9.62
Benedict 2000	TX	47.9	6.6	14.3	2.1	110	6.6
	SP	41.4	12.2	13.4	2.2	106.3	10
	HC	43.5	9.4	13.9	1.8	109.7	5.3
Chiaravalloti 2002	TX	45.4	8.4	15.3	2.2	100.9	11.6
	HC	41.2	11	14.9	2.1	101.9	9.1
Chiaravalloti 2005	TX	45.14	13.78	14.64	2.71	?	x
	CG	46	9.28	15.04	2.82	?	x
Chiaravalloti 2003	TX	45.6	11.45	15.2	2.47	x	x
	HC	42.3	11.58	15.5	2.4	x	x
Jonsson 1993	TX	46.1	7.3	10.9	2	x	x
	CG	43	9	12.2	2.9		
Lincoln 2002	TX	40.5	x	16	x	101	x
	AG	43	x	16	x	106	x
	CG	43	x	16	x	103	x
Mendoza 2001	TX	54.6	x	x	x	x	x
	CG	64.7	x	x	x	x	x
Solari 2004	TX	46.2	9.2	x	x	x	x
	CG	41.2	10.6	x	x	x	x
Tesar	TX	45.3	9.2	x	x	x	x
	CG	46.9	11.2	x	x	x	x
Average		*45.3*	*9.9*	*14.3*	*2.3*	*103.8*	*8.7*
Studies Reporting		*11*	*8*	*7*	*6*	*4*	*3*

Table 4. Overview of MS-related factors in reviewed cognitive remediation studies in multiple sclerosis.

	Years since Dx	SD	Years since Sx Onset	SD	Physical Sx	SD	Physical Sx Measure
Allen 1995	18	x	x	x	x	x	x
Allen 1998	x	x	x	x	4	1.71	EDSS
Benedict 2000	x	x	x	x	4.9	2.2	EDSS
	x	x	x	x	5.1	2.6	EDSS
	x	x	x	x	x	x	x
Chiaravalloti 2002	10.65	8.35	x	x	2.07	x	AI
	x	x	x	x	x	x	x
Chiaravalloti 2005	14.01	8.44	x	x	3.21	2.81	AI
	8.35	5.01	x	x	2.43	2.62	AI
Chiaravalloti 2003	9.22	7.3	x	x	4.5	2.4	EDSS
	x	x	x	x	x	x	x
Jonsson 1993	x	x	15	11.2	5.6	1.7	EDSS
	x	x	15.1	8.5	5.5	2.5	EDSS
Lincoln 2002	x	x	x	x	3	x	EDSS
	x	x	x	x	4	x	EDSS
	x	x	x	x	4	x	EDSS
Mendoza 2001	x	x	31	9.1	x	x	x
	x	x	27.7	10.4	x	x	x
Solari 2004	x	x	x	x	3	x	EDSS
	x	x	x	x	4	x	EDSS
Tesar	8	4.2	x	x	4.5	1.7	EDSS
	10.4	7.2	x	x	4.4	1.9	EDSS
Average	*11.2*	*6.8*	*22.2*	*9.8*	*4.4*	*2.2*	*7ED:1AI:2X*
Studies Reporting	*4*	*3*	*2*	*2*	*9*	*6*	
Avg. EDSS					*4.8*	*2.2*	
Avg. AI					*3.5*	*2.6*	

Table 5. Overview of MS type in reviewed cognitive remediation studies in multiple sclerosis.

	MS Dx Measure	PP	SP	RR	PR
Allen 1995	?	?	?	?	?
Allen 1998	Poser	?	?	?	?
Benedict 2000	?	1	14	0	0
Chiaravalloti 2002	?	?	?	?	?
Chiaravalloti 2005	Poser	4	7	17	0
Chiaravalloti 2003	Poser	18	25	21	0
Jonsson 1993	Schumacher	9	25	21	0
Lincoln 2002	Poser	19	94	107	0
Mendoza 2001	?	?	?	?	?
Solari 2004	Poser	3	35	39	0
Tesar 2005	Poser	0	6	13	0
Number of studies	7	7	7	7	7
Total number		*54*	*206*	*218*	*0*

Table 6. Overview of rule-outs in reviewed cognitive remediation studies in multiple sclerosis.

	Hx Neuro Conds.	Hx Drug/ Alcohol	Non-MS Psych. Dx	MS Relapse PRE	MS Relapse DURING	Meds held constant	Age over 65 years	Severe sensory/ motor deficits
Allen 1995	x	x	x	x	Yes	Yes	x	x
Allen 1998	x	x	x	x	x	x	x	x
Benedict 2000	Yes	Yes	Yes	Yes	x	x	x	x
Chiaravalloti 2002	Yes	Yes	Yes	Yes	x	x	x	x
Chiaravalloti 2005	Yes	Yes	Yes	Yes	x	x	Yes	x
Chiaravalloti 2003	Yes	Yes	Yes	Yes	x	x	Yes	x
Jonsson 1993	Yes	Yes	Yes	x	Yes	Yes	Yes	Yes
Lincoln 2002	x	x	x	x	x	x	x	x
Mendoza 2001	Yes	x	Yes	x	x	x	x	x
Solari 2004	x	x	Yes	Yes	Yes	Yes	Yes	x
Tesar 2005	Yes	Yes	Yes	Yes	x	Yes	Yes	x
Sum	7	6	8	6	3	4	5	1

Table 7. Overview of objective cognitive measures in reviewed cognitive remediation studies in multiple sclerosis.

Objective Measures	IQ Measure	WAIS-R Verbal Subtests	Visual Spatial Measure	Language Measure	WMS-R Subtests	List learning Measure	Memory Measure	Visual Memory Measure
Allen 1995	WAIS-R	All	x	x	All	CVLT	BSRT	x
Allen 1998	WAIS-R	All	x	x	All	x	X	x
Benedict 2000	?	x	CFT, JLO	TT, BNT	x	CVLT	X	BVMT-R
Chiaravalloti 2002	WRAT3 R	DS	x	BNT	LM	x	X	x
Chiaravalloti 2005	WAIS-R V	DS	WAIS-R BD	x	LN	HVLT-R	X	x
Chiaravalloti 2003	X	DS	x	x	x	x	X	x
Jonsson 1993	DART	I, S, V	WAIS-R BD,PC,PA	x	x	uncited	uncited	uncited
Lincoln 2002	NART	All	x	x	x	x	RMT	x
Mendoza 2001	NANART	All	x	BNT	x	HVLT	x	x
Solari 2004	X	x	x	x	x	x	x	"10/36"
Tesar 2005	MWT-B	x	x	x	x	VLT	BSRT	NVLT
Total number	8	8	3	3	4	6	4	4

Table 8. Overview of objective executive functioning measures in reviewed cognitive remediation studies in multiple sclerosis.

Objective Measures	Attention, Processing Speed Measure	Verbal Fluency Measure	Sorting Measure	Other Executive Functioning Measure
Allen 1995	x	x	x	x
Allen 1998	x	x	x	x
Benedict 2000	Trails B, PASAT	x	WCST	BCT
Chiaravalloti 2002	TMT, PASAT	COWAT/Animals	WCST	Stroop
Chiaravalloti 2005	TMT,SDMT,PASAT	COWAT/Animals	x	x
Chiaravalloti 2003	PASAT	x	x	x
Jonsson 1993	TMT, PASAT	COWAT/Animals	uncited	Stroop
Lincoln 2002	x	x	uncited	Stroop
Mendoza 2001	x	COWAT	x	Stroop
Solari 2004	SDMT, PASAT	uncited	x	x
Tesar 2005	DAUF	x	CKV	x
Total number	7	5	5	5

Table 9. Overview of subjective measures in reviewed cognitive remediation studies in multiple sclerosis.

Subjective Measures	Personality Measure	Aggression Measure	Depression Measure	Anxiety Measure	Fatigue Measure
Allen 1995	x	x	BDI	BAI	x
Allen 1998	x	x	BDI	x	x
Benedict 2000	HES; NEO-PI	TBI Scale	BDI	x	x
Chiaravalloti 2002	x	x	BDI	STAI	x
Chiaravalloti 2005	x	x	BDI	STAI	x
Chiaravalloti 2003	x	x	x	x	x
Jonsson 1993	x	x	BDI	STAI	x
Lincoln 2002	x	x	GHQ-28	x	x
Mendoza 2001	x	x	BDI	x	x
Solari 2004	x	x	CMDI	x	x
Tesar 2005	x	x	BDI	x	FIS
Total number	1	1	10	4	1

Table 10. Overview of subjective measures of quality of line in reviewed cognitive remediation studies in multiple sclerosis.

Subjective Measures	Everyday Performance Measure	Everyday Memory Measure	Functional Impairment Measure	Quality of Life Measure
Allen 1995	x	x	x	x
Allen 1998	RBMT	MQ	x	x
Benedict 2000	x	x	x	x
Chiaravalloti 2002	x	x	x	x
Chiaravalloti 2005	x	MFQ	x	x
Chiaravalloti 2003	x	x	x	x
Jonsson 1993	x	x	x	x
Lincoln 2002	TEA,BADS,DEX	EMQ	EADL; GNDS	SF-36; MSQOL-54
Mendoza 2001	x	x	x	x
Solari 2004	x	x	x	MSQOL-54
Tesar 2005	x	x	x	x
Total number	2	3	1	2

Table 11. Overview of intervention factors in reviewed cognitive remediation studies in multiple sclerosis.

Subjective Measures	Total # of Sessions	Length of Session in Hrs	# of Sessions per week	Follow-Up Session at	Average # Tx Hrs	Drop-Outs	Drop-Out reasons listed
Allen 1995	10	?	?	4 wks	?	0	x
Allen 1998	15	0.5	2-Jan	x	?	2	x
Benedict 2000	12	1	1	2 wks	?	?	x
Chiaravalloti 2002	12	1	1	30m, 1wk	?	?	x
Chiaravalloti 2005	8	0.75	2	30, 90 m	?	1	Yes
Chiaravalloti 2003	1	?	1	1 wk	?	?	x
Jonsson 1993	?	1.25	3	24 wks	17.2	8	Yes
Lincoln 2002	?	?	?	16, 32 wks	?	17	Yes
Mendoza 2001	70	?	7	x	?	1	Yes
Solari 2004	16	0.75	2	16 wks	?	7	Yes
Tesar 2005	12	1.5	1	4 wks	?	1	Yes
Total number	9	7	9	8	1	9	6
Average number	*17*	*1*	*2*	*11*		*5*	

Table 12. Continued overview of intervention factors in reviewed cognitive remediation studies in multiple sclerosis.

	Intervention	Comput.	Technique Described?	RA Involved	RA Training	Individ. Format?	Sign. Other ?
Allen 1995	List/Face Tasks	Yes	Yes	Yes	X	Yes	x
Allen 1998	List/Face Tasks	Yes	Yes	Yes	X	Yes	x
Benedict 2000	Neuropsych Counseling	x	Yes	Yes	X	Yes	Yes
Chiaravalloti 2002	Generation Effect	x	Yes	Yes	X	Yes	x
Chiaravalloti 2005	List Task	Yes	Yes	Yes	X	Yes	x
Chiaravalloti 2003	Repetition Effect	x	Yes	Yes	X	Yes	x
Jonsson 1993	Cognitive Training	x	Yes	Yes	X	Yes	x
Lincoln 2002	Cognitive Rehab	x	x	x	X	Yes	Yes
Mendoza 2001	Memory Notebook	x	Yes	Yes	Yes	Yes	x
Solari 2004	RehaCon	Yes	Yes	Yes	X	Yes	x
Tesar 2005	RehaCon	Yes	Yes	Yes	X	Yes	x
Total number		5	10	10	1	11	2

Table 13. Participant demographic test data.

Demographic Data	MNG	SG		T-Test
Age	45.67(7.37)	44.50(3.61)	(10)	p=0.74
Years of education	14.83(2.64)	15.33(1.51)	(10)	p=0.70
IQ est (NAART)	111.16(10.20)	111.85(3.33)	(10)	p=0.88
AI	2.00(1.41)	3.20(3.83)	(9)	p=0.49
MSFC	0.05(0.69)	0.12(0.71)	(7)	p=0.88
RMBT	20.50(2.35)	19.00(3.58)	(10)	p=0.44
Female/Male	4/2	4/2	(10)	p= 1.00
Ethnicity: Caucasian/other	6/0	6/0	(10)	p=1.00
Course: RR/PP/SP/RP	5/1/0/0	5/1/0/0	(10)	p=1.00
Emp/Unemp/Retired/Self-Emp	2/3/0/1	2/2/1/1	(10)	p=0.80
Inpatient/Outpatient	0/6	0/6	(10)	p=1.00
Avg # Tx Sessions	6.67(.52)	6.17(.75)	(10)	p=0.21
Avg # Tx Hours	10.00(.75)	9.25(1.13)	(10)	p=0.21

Table 14. Participant neuropsychological test data.

Neuropsychological Data	MN	SG	Btw-Group T-Test	
Language				
DKEFS phonetic	43.33(7.89)	34.67(18.33)	(10)	p=0.31
DKEFS semantic	45.50(6.47)	42.83(9.95)	(10)	p=0.60
Boston Naming Test	56.83(2.40)	56.67(1.53)	(10)	p=0.92
Spatial				
Judgment of Line Orientation	26.17(3.87)	26.50(3.51)	(10)	p=0.88
Memory				
CVLT-R T1	7.67(1.51)	7.00(2.19)	(10)	p=0.55
CVLT T5	12.83(1.94)	12.83(.98)	(10)	p=1.00
CVLT T1:T5	55.67(8.19)	53.67(8.38)	(10)	p=0.67
CVLT Short Delay	11.00(3.35)	11.17(2.93)	(10)	p=0.93
CVLT Long Delay	12.00(2.76)	11.67(2.42)	(10)	p=0.83
BVMT-R T1	5.80(2.17)	5.83(3.19)	(9)	p=0.99
BVMT T3	10.20(1.30)	9.67(1.75)	(9)	p=0.59
BVMT T1:T3	25.80(4.60)	22.17(7.76)	(9)	p=0.38
BVMT Delayed	10.40(1.34)	9.17(2.04)	(9)	p=0.28
Executive				
SDMT-Oral	55.20(3.11)	51.67(11.98)	(10)	p=0.54
PASAT 3.0	44.75(19.36)	45.50(12.72)	(10)	p=0.94
PASAT 2.0	39.75(8.42)	34.67(11.34)	(10)	p=0.47
DKEFS Sort Total	10.00(3.16)	11.00(3.03)	(9)	p=0.61
DKEFS Descr Total	40.20(13.72)	43.33(10.75)	(9)	p=0.68
DKEFS Recog	38.60(14.44)	38.17(9.87)	(9)	p=0.95
DKEFS VF Switching	14.00(3.35)	11.17(4.96)	(10)	P=0.27

Table 15. Summary of assessment measures.

Initial Assessment (Neuropsychological)	Second Assessment (Pre-Treatment)	Mid-Treatment Assessment	Post Treatment Assessment
MACFIMS	RBMT	5PMT	CES-D
-COWAT	EMQ	5RMT	FSS
-JLO	FAMS-2		EMQ
-CVLT-II	STAI		FAMS-2
-BVMT-R	5PMT		5PMT
-PASAT	5RMT		5RMT
-SDMT			EMQ
-D-KEFS Sort			STAI
MSFCM			
NAART			
CES-D			
FSS			

Table 16. Participant pharmaceutical treatment data.

MS Pharmaceutical Treatment	Memory Notebook Group	Supportive Psychotherapy
Interferon beta	3	2
Tysabri	1	2
Copaxone	1	1
No Treatment	1	1

Figure 1: Self-reported everyday memory failures as measured with the Everyday Memory Questionnaire (EMQ) as function of Group (Memory Notebook Group [MNG] and Supportive Psychotherapy [CG]) across Time (Pre-Treatment and Post Treatment).

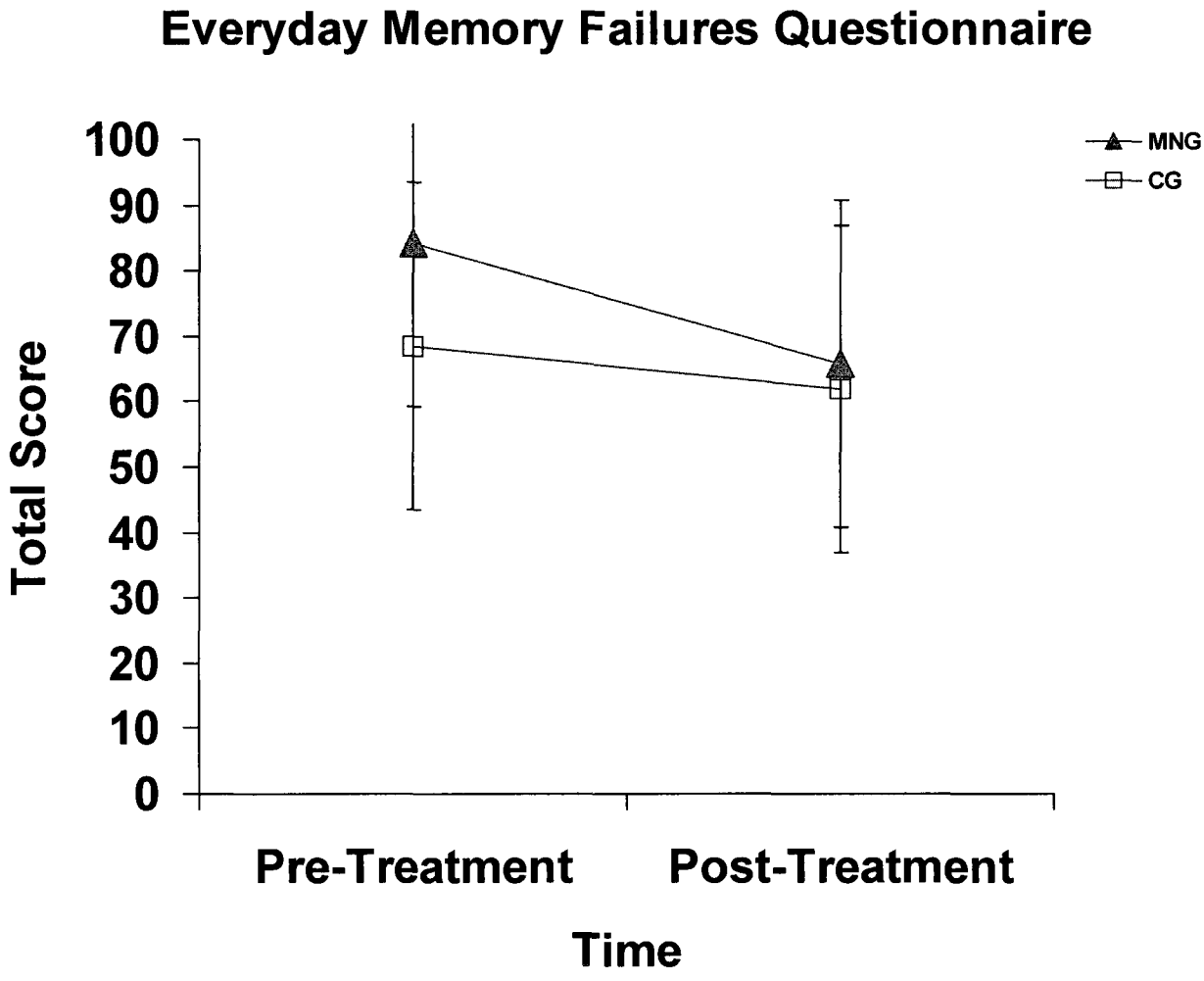


Figure 2: Self-reported everyday memory failures as measured with the Everyday Memory Questionnaire (EMQ) wherein, instead of using the total score, the total number of items endorsed (i.e., scores greater than zero) was tallied as function of Group (Memory Notebook Group [MNG] and Supportive Psychotherapy [CG]) across Time (Pre-Treatment and Post Treatment).

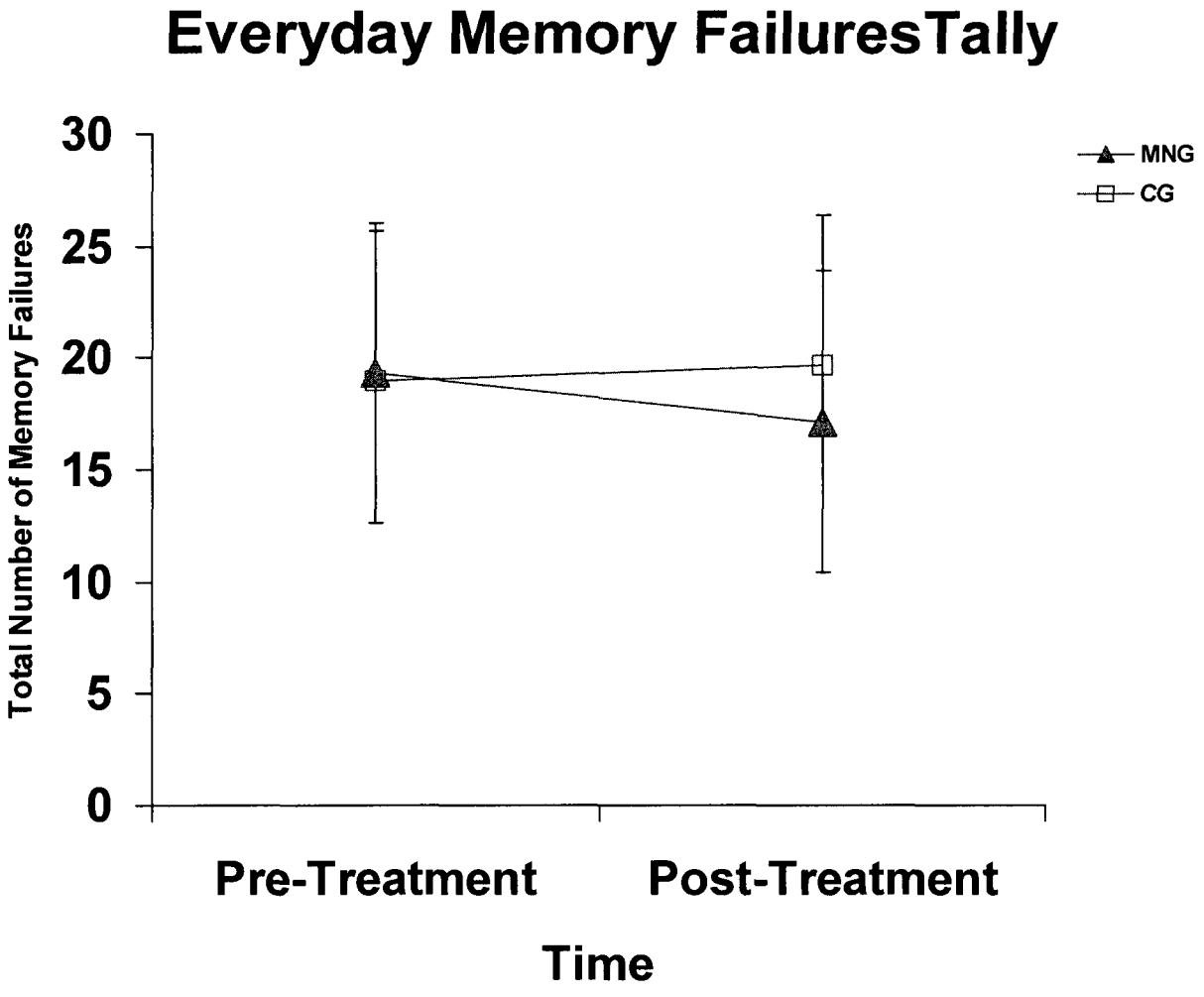


Figure 3: Self-reported depression symptoms as measured with Center for Epidemiologic Studies Depression Scale (CES-D) as function of Group (Memory Notebook Group [MNG] and Supportive Psychotherapy[CG]) across Time (Pre-Treatment and Post Treatment).

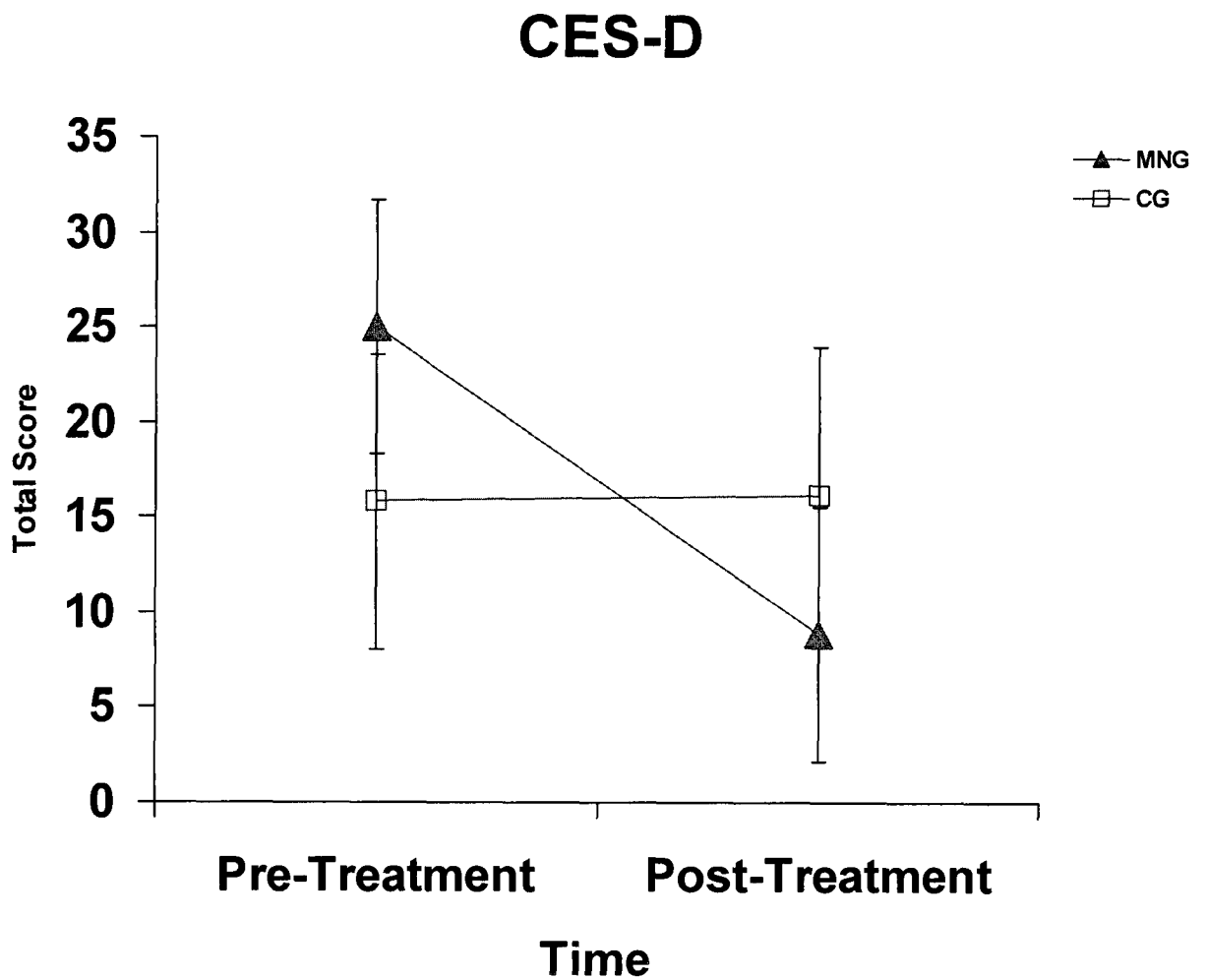


Figure 4: Total number of items recalled on the Prospective Memory Task as function of Group (Memory Notebook Group [MNG] and Supportive Psychotherapy[CG]) across Time (Pre-Treatment and Post Treatment).

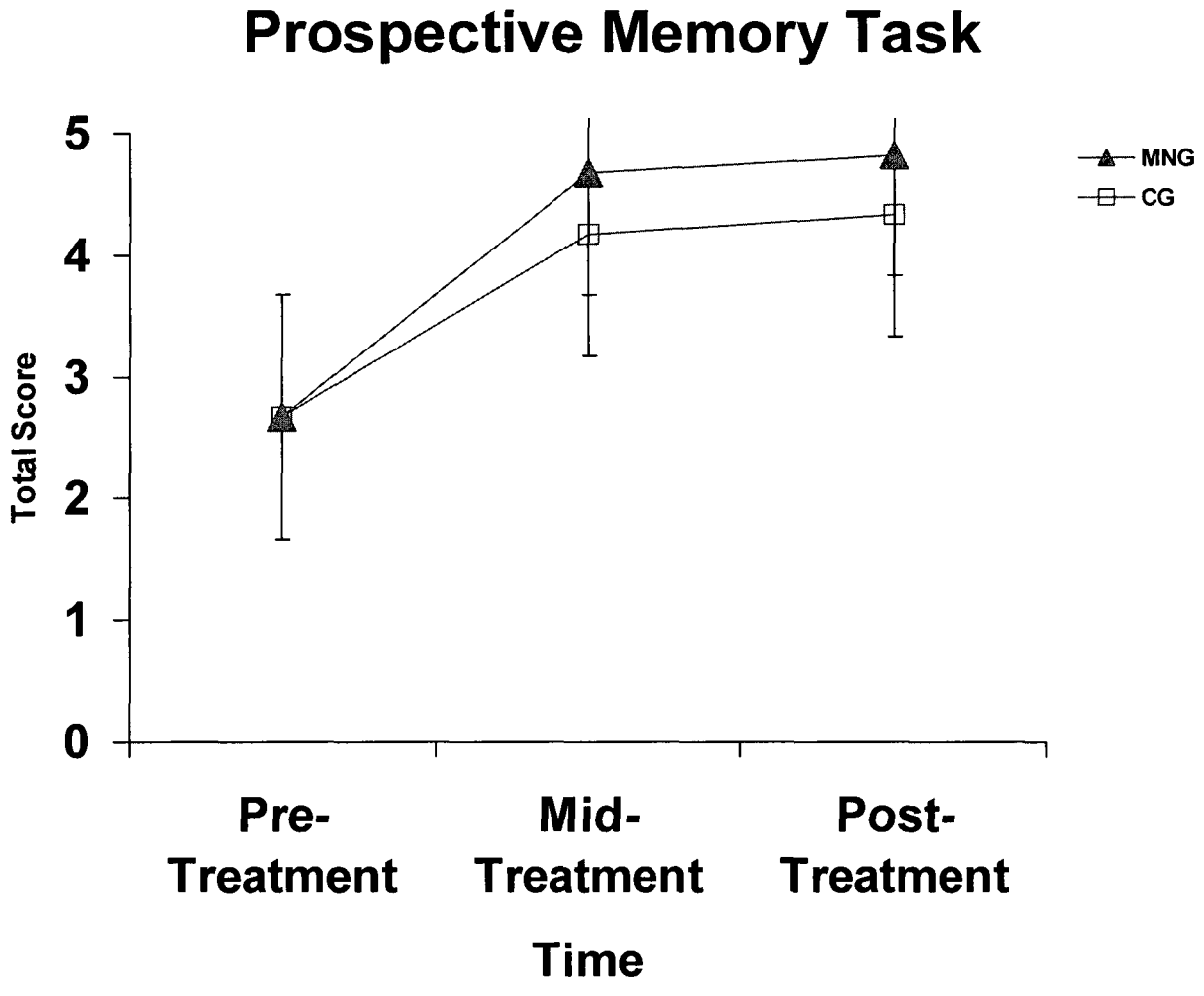
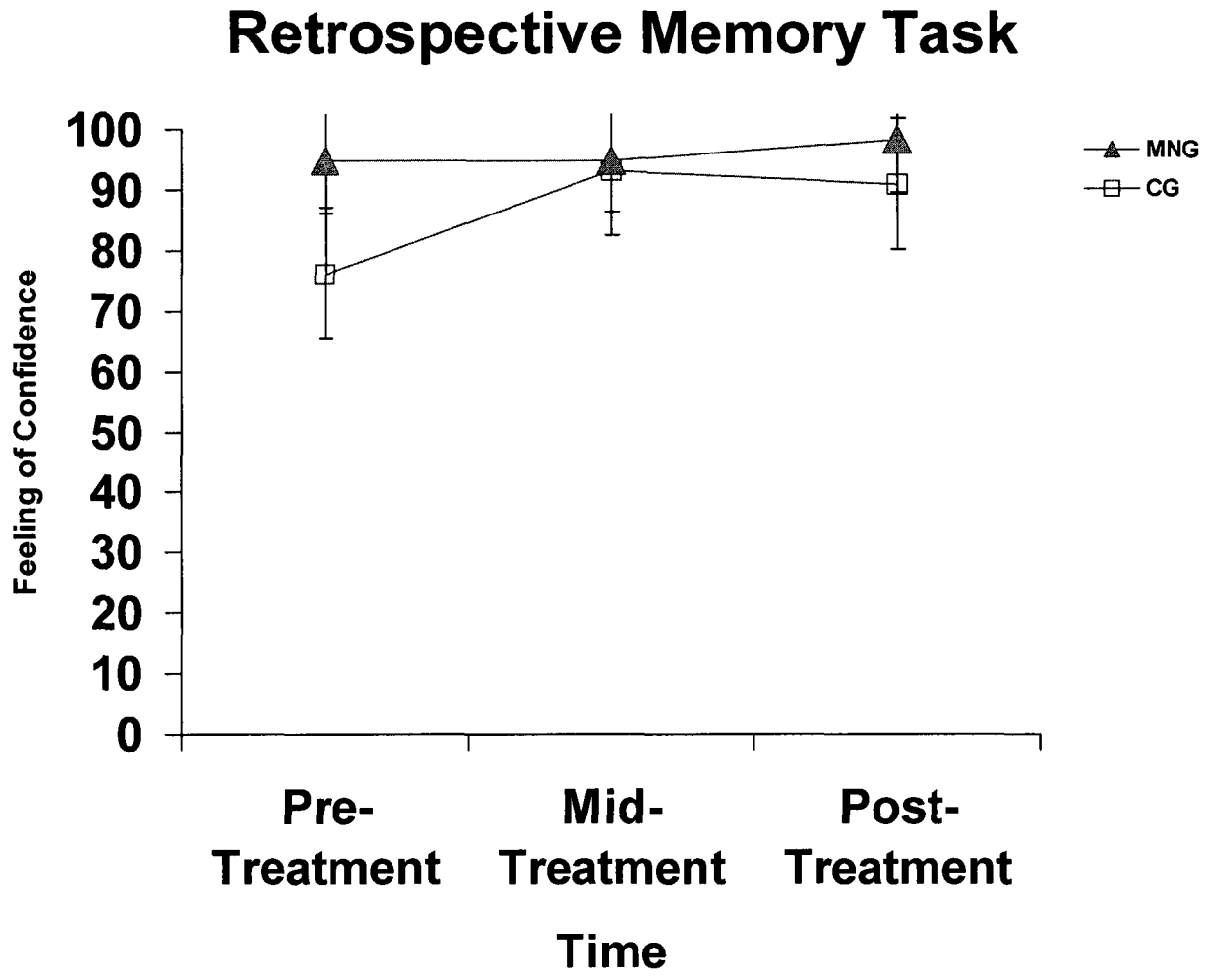


Figure 5: Feeling of confidence (0-100%) for ability to remember completed activities on the Retrospective Memory Task as function of Group (Memory Notebook Group [MNG] and Supportive Psychotherapy[CG]) across Time (Pre-Treatment and Post Treatment).



APPENDIX

Appendix A: Recommendations for future cognitive remediation research with multiple sclerosis patients.

1. Participant Recommendations:
    a. In regards to the presence of MS:
        i. Define MS using referenced criteria (e.g., Posner).
        ii. Count the number of participants with each type of MS (e.g., PP, RR, SP)
        iii. Report the duration since symptom onset and since diagnosis.
    b. In regards to the presence of cognitive impairment:
        i. Define minimum standards of cognitive impairment using referenced criteria
        ii. Define maximum standards of cognitive impairment using referenced criteria
        iii. Define the severity of the cognitive impairment (e.g., mild, moderate, severe)
        iv. Consider utilizing both performance and self-report measures of cognition; justify such measures
    c. In regards to the nature of participant variables:
        i. Define physical and sensory disability using referenced criteria (e.g., EDSS, Ambulatory Index)
        ii. Define living situation as inpatient or outpatient
        iii. Using justified measures, measure the degree and range of 1) depression 2) anxiety 3) functional impairment; 4) quality of life; and 5) fatigue.

d. Special considerations for the control group (CG)
    i. Ideally, control groups will be composed of individuals with MS
    ii. Pseudo-treatments should not have a treatment effect
    iii. If control group is engaging in modified cognitive remediation or supportive intervention, consider including an additional wait-list control group to examine "placebo" effects
    iv. A secondary control group with healthy controls could be included
    v. Control and experimental groups should be matched on the following variables:
        1. age
        2. education
        3. premorbid IQ (using referenced criteria)
        4. M/F ratio
        5. disease duration
        6. physical disability
        7. neuropsychological testing and intervention hours
        8. employment status
        9. living situation (inpatient or outpatient)
        10. type of MS (PP, SP, RR, PR)
        11. memory impairment severity
e. The following exclusionary criteria could be considered:
    i. History of other neurological disease, including TBI
    ii. Drug/alcohol abuse/dependence

iii. Non-MS related psychiatric disorders

iv. MS relapse/corticosteroid treatment initiation within one month of the start of the study, and for the duration of the study

v. Over the age of 60 years; under the age of 18 years

vi. Sensory/ upper limb physical disability interfering with intervention participation

vii. Disallowing or measuring the initiation of psychotropic drugs or drugs for spasticity, tremor, bladder disturbances and fatigue, requiring doses and schedules to be held constant

f. Number and reasons for participant drop-outs should be provided

2. Intervention Recommendations:

a. Describe method for randomizing participants

b. Describe method for assuring double-blindness and provide a blindness test

c. Justify whether intervention will follow an individual or group format

d. Justify whether intervention will include a close relative or friend and describe the role of this individual

e. Justify intervention schedule in terms of hours/days/sessions/weeks and report averages for these variables

f. Justify and report the location of intervention (e.g., inpatient/outpatient)

g. Justify and report degree of supervision (e.g., % hours directly supervised by trained facilitator vs. individual work)

h. Justify and report training protocol of facilitators

i. Specify intervention protocol for experimental and control group, including theoretically and research-based principles

j. Report the prospectively defined endpoint, including primary and secondary outcomes (e.g., cognitive, depression, anxiety, functional ability, quality of life, and/or fatigue measures).

k. Report prospectively defined follow-up points, including 6-mos and preferably 1-year.

3. Results

a. Report and justify statistical procedures

b. Describe changes in terms of statistical and clinically-relevant changes

c. Describe within vs. across-group differences

d. Report maintenance or generalization of any reported changes

Appendix B: A Semi-structured interview to measure environmental demands.
Participant #_____ Date: _____
Administrator:_____

Do you experience memory problems?
What kinds of memory problems do you experience in your home? What kinds of demands are really stressful you at home?

Do you work? What kinds of memory problems do you experience at work? What kinds of demands are really stressful you at work?

Do you attend school? What kinds of memory problems do you experience at school? What kinds of demands are really stressful you at school?

Do you participate in extracurricular hobbies or groups? What kinds of memory problems do you experience at extracurricular settings? What kinds of demands are really stressful for you during these extracurricular events?

Any other memory problems?

Appendix C: Phone Questionnaire for the Memory Notebook Group.

Participant #_____ Date: _____

Phone call #_____ Administrator:_____

May I please speak to _____. This is _____ calling from Washington State University in regards to the Memory Notebook and MS study.

How is the memory notebook going?

_____

_____

_____

_____

Have you used it today? _____

_____

_____

_____

Have you had any problems with the notebook? Please describe them _____

_____

_____

_____

Problem #1_____

Solution: _____

_____

_____

Problem #2_____

Solution: _____

_____

_____

Problem #3_____

Solution: _____

_____

_____

Problem #4_____

Solution: _____

_____

_____

Thanks for your participation! Have a great day!!

Appendix D: Phone Questionnaire for the Supportive Therapy Control Group.

Participant #_____ Date: _____
Phone call #_____ Administrator:_____

This is _____ calling from Washington State University in regards to the Memory and MS Support Group study. May I please speak to _____?

Have you had any memory problems today? Please describe them

_____
_____
_____
_____

Problem #1_____
_____
_____
_____

Problem #2_____
_____
_____
_____

Problem #3_____
_____
_____
_____

Problem #4_____
_____
_____
_____

Thanks for your participation! Have a great day!!

Appendix E: Left-Sided Memory Notebook.

5:00 5AM	:00			17:00 5PM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
6:00 6AM	:00			18:00 6PM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
7:00 7AM	:00			19:00 7PM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
8:00 8AM	:00			20:00 8PM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
9:00 9AM	:00			21:00 9PM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
10:00 10AM	:00			22:00 10PM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
11:00 11AM	:00			23:00 11PM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
12:00 12PM	:00			24.00 12PM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
13:00 1PM	:00			1:00 1AM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
14:00 2PM	:00			2:00 2AM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
15:00 3PM	:00			3:00 3AM	:00		
	:15				:15		
	:30				:30		
	:45				:45		
16:00 4PM	:00			4:00 4AM	:00		
	:15				:15		
	:30				:30		
	:45				:45		

Appendix F: Right-Sided Memory Notebook.

THINGS TO DO	

Appendix G = Abbreviations List.

5PMT = 5 Prospective Memory Tasks
9HPT = 9-Hole Peg Test
AI = Ambulation Index
ANCOVA = analysis of covariance
BAI = Beck Anxiety Inventory
BDI = Beck Depression Inventory
BNT = Boston Naming Test
BRBNT = Brief Repeatable Battery of Neuropsychological Tests
BSRT = Buschke Selective Reminding Task
BVMT-R = Brief Visuospatial Memory Test-Revised
CCSE = Cognitive Capacity Screening Examination
CES-D = Center for Epidemiologic Studies-Depression Scale
CFT = Complex Figure Test
CG = Control Group
CMDI = Chicago Mood Depression Inventory
CNS = Central Nervous System
COWAT = Controlled Oral Word Association Test
CT = Computed Tomography
CVLT = California Verbal Learning Test
CVLT-II = California Verbal Learning Test, 2nd Ed.
DRS = Dementia Rating Scale
DST = D-KEFS Sorting Test
EADL = Extended Activities of Daily Living
EDSS = Expanded Disability Status Scale
EMQ = Everyday Memory Questionnaire
FAMS = Functional Assessment of Multiple Sclerosis
FAMS-2 = Functional Assessment of Multiple Sclerosis, Version 2
FIS = Fatigue Impact Scale
FSS = Fatigue Severity Scale
GHQ-28 = General Health Questionnaire
GNDS = Guys Neurological Disability Scale
HC = Healthy Control participants
HES = Hogan Empathy Scale
HVLT-R = Hopkins Verbal Learning Test-Revised
IFN = Interferon Beta
JLO = Judgment of Line Orientation
K-SNAP = Kaufman Short Neuropsychological Procedure
M = Mean
MACFIMS = Minimal Assessment of Cognitive Functioning in Multiple Sclerosis
MFIS = Modified Fatigue Impact Scale
MFQ = Memory Functioning Questionnaire
MMSE = Mini Mental Status Exam
MNG = Memory Notebook Group
MQ = Memory Questionnaire
MRI = Magnetic Resonance Imaging
MS = Multiple Sclerosis
MSFCM = Multiple Sclerosis Functional Composite Measure
MSQOL-54 = MS Quality of Life- 54 scale
MTG = Memory Training Group
MWT-B = Multiple Vocabulary Test-B (German)
NAART = North American Adult Reading Test
NART = National Adult Reading Test
NCT = Neuropsychological Compensatory Training Group
NEO-PI = NEO Personality Inventory
NSP = Non-Specific Supportive Psychotherapy Group
NTG = Neurological Training Group
PASAT = Paced Auditory Serial Addition Test
PP = Primary-Progressive MS
PR = Progressive-Relapsing MS
QOL = Quality of life
RBMT = Rivermead Behavioral Memory Test
RBMT-TOTAL = composite score for RBMT
RIS = Ridiculously Imaged Story technique
RMT = Recognition Memory Test
RR = Relapsing-Remitting MS
SCL-90-R = Symptom Checklist 90—Revised
SD = Standard Deviation
SDMT = Symbol Digit Modalities Test
SF-36 = MOS 36-Item Short-Form Health Survey
SP = Secondary-Progressive MS
SPS = Standardized Profile Score
SR = Spaced Retrieval cognitive technique
SRT = Story Recall Technique
STAI = State Trait Anxiety Inventory

T25W = Timed 25-Foot Walk
TBI = Traumatic Brain Injury
TEA = Test of Everyday Attention
TLA = Total T2 Lesion Area on MRI
TMT = Trail Making Test
WAIS-R = Wechsler Adult Intelligence Scale-Revised
WCST = Wisconsin Card Sorting Test
WMS-R = Wechsler Memory Scale- Revised
WRAT-3 = Wide Range Achievement Test-3

Appendix H. Everyday Memory Assessment Measure.

Everyday Memory Assessment Measure

Please consider the past seven days when answering the following questions:

Using a scale of 0 to 6 with N/A; 0 = not at all; 4 = some of the time; 7 = most of the time; in the past week to what extent have you been able to:

1. keep track of chores and tasks you have to-do
2. remember to do things people have asked you to do
3. prioritize your goals
4. plan your schedule according to your goals
5. reflect on your values and interests
6. keep track of important information
7. made an organized record of medical or health information
8. feel in control of your schedule
9. been able to remember the tasks you have completed
10. been able to remember tasks you have not completed
11. feel that others can depend on you to remember things
12. feel hopeful that you can overcome your memory deficits
13. can remember people's names that you have met recently
14. can solve problems in an organized manner
15. participate in conversations with the confidence that you know the relevant details
16. recall the important details of conversations
17. recall the important details of work presentations and/or school lectures
18. keep track of appointments
19. have feelings of confusion
20. have feelings of disorientation to time
21. feel a sense of purpose
22. overcome your memory problems
23. organize your schedule
24. have hope in your ability to succeed

Appendix I. Participants' comments and feedback about the treatment.

Quotes at the end of the memory notebook group:
-It's like carrying around my brain with me
-I enjoyed the goal-generating section; it has help me get a new perspective on my life
-It has helped to keep better track of assignments and remember the lectures more easily
-I can transfer my notes from work into here and take them home with me
-I can have better discussions with my husband because I can look back at my notes
-I can remember appointments by looking in my notebook and surprise everyone
-Sometimes I don't like to look in it because it reminds what I have to do
-I can jot down the notes of phone calls that I usually forget
-It sure takes me a long time to get things done!
-I realize I don't have much of a life
-When people see my notebook they joke about needing one
-Helps with problem-solving; it gives me a place to sort-out my thoughts
-Helps keep me on track
- Keeps me motivated
-Helps me plan
-With the notebook, I can spread-out me tasks; keeps me more even-keeled
-loved it!
-I can be very organized, and remember things
-I can remember people's names by looking them up in the notebook
-It's kind of big and a little awkward to carry around
-I can find it in my stuff because it's so big

Quotes at the end of the support group:
-I was searching for a support group to join, so this really fit.
-I felt like I could relate to what people were saying
-I wanted to meet other people like me
-I enjoyed sharing
-I learned a bit from everybody
-This group increased my confidence
-I learned that I'm not really nuts!
-very inspiring
-I appreciated learning about the brain structures
-The therapist was good at taking information and re-interpreting it
- The therapist was good at teaching
-I felt supported by others
-This group was calming and accepting
-I learned to come to terms with my losses
-It was a quiet break from everything; my little time
-I spent the whole time wondering what group am I in?
-I would never have come without someone encouraging me
-I was skeptical because I thought it would be unhelpful or a waste of time
-You gave us hope. Thank you.

Appendix J. Statisitics output summary.

Measure		MNG	CG		
CESD	1. Pre	25.00(16.77)	15.83(10.53)	(10)	p=0.28
	2. Post	8.83(8.15)	16.17(7.78)	(10)	p=0.14
Repeated Meas. GLM		CESD	F(1,9)= 7.99, p=0.02**		
		CESD* Group	F(1,9) = 8.69, p=0.02**		
EMQ	1. Pre	84.17(50.82)	65.83(37.24)	(10)	p=0.49
	2. Post	68.33(42.22)	61.83(44.44)	(10)	p=0.80
Repeated Meas. GLM		EMQ	F(1,9) = 3.62, p = 0.09		
		EMQ* Group	F(1,9) = 1.288, p = 0.28		
EMQTALLY	1. Pre	19.33(6.71)	19.00(7.32)	(10)	p=0.94
	2. Post	17.16(7.75)	19.67(7.31)	(10)	p=0.58
Repeated Meas. GLM		EMQ T	F(1,10) = 1.58, p = p=0.39		
		EMQ T* Group	F(1,10) = 5.127, p = p=0.12		
5PMT	1. Pre	2.67(2.25)	2.67(2.16)	(10)	p=1.00
	2. Mid	4.67(0.82)	4.17(0.98)	(10)	p=0.36
	3. Post	4.83(0.41)	4.33(0.82)	(10)	p=0.21
Repeated Meas. GLM		PMT	F(2,9) = 7.29, p = 0.004*		
		PMT*Group	F(2,9) = 0.14, p = 0.88		
		Post Hoc			
		PMT(pre)	$t(11) = -3.29.$, p = 0.007		
		PMT(mid)	$t(11) = -2.59.$, p = 0.025		
		PMT(end)	$t(11) = -0.69.$, p = 0.504		
5RMT	1. Pre	94.70(8.06)	76.17(26.76)	(10)	p=0.14
	2.Mid	94.90(8.58)	93.33(10.17)	(10)	p=0.78
	3. Post	98.33(2.66)	91.00(12.82)	(10)	p=0.20
Repeated Meas. GLM		RMT	F(2,9) = 4.62, p = 0.04*		
		RMT	F(2,9) = 1.63, p = 0.25		
		Post Hoc			
		RMT(pre)	$t(11) = -2.62.$, p = 0.024		
		RMT(mid)	$t(11) = -1.75.$, p = 0.108		
		RMT(end)	$t(11) = -0.26.$, p = 0.803		
STAI State	1. Pre	32.50(11.73)	37.17(11.87)	(10)	p=0.51
	2. Post	29.33(5.01)	36.50(12.68)	(10)	p=0.23
Repeated Meas. GLM		State	F(1,10) = 0.332, p = 0.58		
		State * Group	F(1,10) = 0.141, p = 0.72		
STAI Trait	1. Pre	30.67(6.02)	42.67(13.55)	(10)	p=0.08
	2. Post	34.83(11.72)	41.67(12.52)	(10)	p=0.35
Repeated Meas. GLM		Trait	F(1,10) = 0.847, p = 0.38		
		Trait * Group	F(1,10) = 1.303, p = 0.28		

Measure		MNG	CG		
FAMS-2	1. Pre	48.83(33.38)	96.83(41.75)	(10)	p=0.05*
	2. Post	69.17(37.29)	96.50(44.76)	(10)	p=0.27
Repeated Meas. GLM		FAMS	F(1,9) = 1.92, p = 0.20		
		FAMS*Group	F(1,9) = 2.05, p = 0.18		
FSS	1. Pre	53.17(8.59)	48.67(13.59)	(10)	p=0.51
	2. Post	44.17(17.17)	48.33(13.91)	(10)	p=0.65
Repeated Meas. GLM		FSS	F(1,8) = 1.45, p = 0.26		
		FSS * Group	F(1,8) = 1.25, p = 0.29		