PROCESSING SPEED AND WORKING MEMORY TRAINING IN MULTIPLE SCLEROSIS: A BLINDED RANDOMIZED CONTROLLED TRIAL

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PROCESSING SPEED AND WORKING MEMORY

TRAINING IN MULTIPLE SCLEROSIS:

A BLINDED RANDOMIZED

CONTROLLED TRIAL

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ABSTRACT

Between 40-65% of patients with multiple sclerosis (MS) experience cognitive deficits associated with the disease. The two most common areas affected are information processing speed and working memory. Information processing speed has been posited as a core cognitive deficit in MS, and working memory has been shown to impact performance on a wide variety of domains for MS patients. Currently, clinicians have few reliable options for addressing cognitive deficits in MS. The current study aimed to investigate the effect of computerized, home-based cognitive training focused specifically on improving information processing speed and working memory for MS patients. Participants were recruited and randomized into either the Active Training or Sham Training group, tested with a neurocognitive battery at baseline, completed six weeks of training, and then were again tested with a neurocognitive battery at follow-up. After correcting for multiple comparisons, results indicated that the Active Training group scored higher on the Paced Auditory Serial Addition Test (a test of information processing speed and attention) following cognitive training, and data trended toward significance on the Controlled Oral Word Associations Task (a test of executive functioning), Letter Number Sequencing (a test of working memory), Brief Visuospatial Memory Test (a test of visual memory), and the Conners' Continuous Performance Test (a test of attention). Results provide preliminary evidence that cognitive training with MS patients may produce moderate improvement in select areas of cognitive functioning. Follow-up studies with larger samples should be conducted to determine whether these results can be replicated, and also to determine the functional outcome of improvements on neurocognitive tests.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the College of Arts and Sciences have examined a thesis titled "Processing Speed and Working Memory Training in Multiple Sclerosis: A Blinded Randomized Controlled Trial," presented by Laura Mitchell Hancock, candidate for the Doctor of Philosophy degree, and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

INTRODUCTION

Multiple Sclerosis (MS) is an autoimmune, demyelinating disease of the central nervous system that affects approximately 1 in 1000 individuals in the United States (Pryse-Phillips & Costello, 2001). MS most frequently afflicts Caucasian women living in temperate climates, and is typically diagnosed in young adulthood (Cree et al., 2004; Wallin, Page, & Kurtzke, 2004). Common symptoms MS patients experience include physical disability, fatigue, pain, sensory disturbances, cognitive difficulties, personality change, anxiety, and depression (Arnett, Barwick, & Beeney, 2008; Benedict, et al, 2005; Bruce & Arnett, 2009; Bruce, Bruce & Arnett, 2007; Bruce, Polen, & Arnett, 2007). There are also significant economic costs associated with MS. Whetten-Goldstein (1998) and colleagues found that the annual cost per person was approximately $34,000, with a national annual cost of $6.8 billion.

Cognitive Deficits in MS

Between 40-65 % of MS patients experience cognitive difficulties associated with the disease (Chiaravalloti & DeLuca, 2008; Rao et al., 1991a; Winkelmann, Engel, Apel, & Zeitl, 2007). Prevalence of cognitive problems in this population represents a significant problem for both patients and treatment providers. Investigators have recorded cognitive problems across several domains, including memory, attention, information processing speed, executive function, mental flexibility, and visuoconstruction ability (Chiaravalloti & DeLuca, 2008; Winkelmann et al., 2007). Overall, cognitive deficits have been associated with problems managing independent activities of daily living, adherence to MS medications, poorer vocational status, difficulty driving, and impaired social functioning (Benedict et al., 2005; Bruce, Hancock, Arnett, & Lynch, 2010; Higginson, Arnett, & Voss, 2000; Rao et al., 1991b). Two of the most commonly noted cognitive deficits are in the areas of information processing speed (Archibald & Fisk, 2000; DeLuca, Johnson, & Natelson, 1993; Demaree et al., 1999; Denney, Lynch, Parmenter, & Horne, 2004; Rao et al., 1989) and working memory (D'Esposito et al., 1996; Lengenfelder, Chiaravalloti, Ricker, & DeLuca, 2003; McCarthy, Beaumont, Thompson, & Peacock, 2005). Information processing speed and working memory are both core cognitive skills that can affect other areas of cognitive performance, including learning, planning, and attention (Amato et al., 2010; Donders & Minnema, 2004; Salthouse, Fristoe, & Rhee, 1996).

Information Processing Speed in MS

Information processing speed is conceptualized as the amount of time needed to process a set amount of information (Kalmar & Chiaravalotti, 2007). It is thought that information processing speed is related to the brain's ability to efficiently and effectively conduct signals between neurons. Nerve signals are conducted along axons that are covered with a myelin sheath that is produced by oligodendrocytes (Compston & Coles, 2008). The disease process in MS involves the development of white matter lesions following damage to the myelin sheath (Compston & Coles, 2008). Lesions in the white matter of the brain have been associated with deficits in cognitive skills, including information processing speed (Pantoni, Poggesi, & Inzitari, 2007).

Initial research in the area of cognitive dysfunction in MS pointed to distributed deficits which were congruent with the multifocal nature of the disease (Rao et al., 1991a). However, recent research has suggested that the core deficit in MS is likely slowed information processing speed (Archibald & Fisk, 2000; DeLuca et al., 2004; Demaree et al., 1999; Denney, Lynch, Parmenter, & Horne, 2004). Prevalence rates for measurable deficits in information processing speed range from 35% to more than 50% (Benedict, Bruce et al., 2006; DeLuca et al., 2004; Nocentini et al., 2006). Deficits in processing speed have also been shown to remain after controlling for accuracy of performance (Demaree et al., 1999). Similarly, researchers have found that slowed processing speed was the only deficit that differentiated patients from healthy controls after removing variance attributable to fatigue and depression (Denney et al., 2004).

Investigators have also suggested that slowed information processing speed affects neuropsychological outcomes on tests that measure a wide variety of functioning (Denney, Gallagher, & Lynch, 2011). Supporting this assertion, researchers found that MS patients with processing speed deficits were able to improve their performance on memory tasks when given additional time to process information in working memory (Arnett, 2004; Leavitt et al., 2011). Similarly, MS patients were able to perform as accurately as healthy controls on a task of working memory when given extra processing time (Lengenfelder et al., 2006). Overall, research in this area seems to indicate that information processing speed is a core skill that affects other areas of cognitive performance and therefore, outcomes on disparate neuropsychological tests.

Working Memory in MS

Working memory, sometimes termed immediate memory, is conceptualized as a short-term, temporary store of information that is actively held in order to complete tasks (Strauss, 2006). Baddeley and Hitch (1974) first posited a multi-dimensional model that explains how the human brain processes information via working memory. This model contains three components: the central executive, the phonological loop, and the visuospatial sketchpad. The central executive (deemed the central control system) modulates the activity of the two slave systems that are responsible for verbal and visual information. More recently, this model was updated to include a third slave system, the episodic buffer, that is responsible for linking information from multiple domains to create integrated information that also includes temporal sequencing (Baddeley, 2000).

Current models of memory suggest that working memory is responsible for visuospatial skills, as well as auditory and verbal span abilities. Additionally, investigators have found evidence that working memory capacity is correlated highly with processing speed (Kyllonon & Christal, 1990). Indeed, using principal components analysis, one study found that working memory and processing speed comprise a single cognitive construct in MS (Benedict, Cookfair et al., 2006). Many different researchers have reported deficits in working memory in MS patients; working memory deficits are considered one of the most common cognitive difficulties in MS (D'Esposito et al., 1996; Lengenfelder et al., 2003; Rao et al., 1991a; Ruchkin et al., 1994).

Intact working memory is vital to overall cognition. Associated with intelligence, working memory is a fundamental cognitive skill that is important in ensuring information can be encoded into long-term memory (Goldman-Rakic, 1993; Jaeggi et al., 2008). Impaired working memory impacts cognitive performance in a wide array of cognitive domains (Lengenfelder et al., 2003; Macniven, Davis, Ho, Bradshaw, & Szabadi, 2008; Parmenter, Shucard, Benedict, & Shucard, 2006). Additionally, it is believed that deficits in working memory disrupt activities related to quality of life, including ability to sustain employment and learn new information (Beatty, Blanco, Wilbanks, Paul, & Hames, 1995; DeLuca, Gaudino, Diamond, Christodoulou, & Engel, 1998).

Treatment of Cognitive Deficits in MS

Currently, options for treating cognitive deficits in MS are limited in number and often have mixed or poorly understood outcomes. Treatment of MS typically involves the utilization of disease-modifying therapies, including glatiramer acetate, interferon beta-1a, interferon beta-1b, and the newly FDA approved fingolimod and teriflunomide. Though no medication can cure the disease, disease-modifying therapies are prescribed both to slow disease progression and reduce exacerbations (Kieseier et al., 2008; Goodin, 2008; Jacobs et al., 1996; Johnson et al., 1995; The IFNB Multiple Sclerosis Study Group, 1993). These drugs have been shown to reduce brain lesion development and by association, cognitive problems inherent in disease activity in the brain (Patti, 2009). However, as Patti (2009) points out in a review article, the direct cognitive benefits of disease-modifying therapies are often not included in drug trials and further investigation into these benefits is warranted.

Traditionally, clinicians combat cognitive deficits by employing rehabilitation strategies (Groth-Marnat, 2000; Keating & Ostby, 1996; Sloan & Ponsford, 1995). For instance, patients may be instructed in the use of memory books to recall past events (episodic memory), or appointment and task lists or electronic reminders to help them remember things they need to do (prospective memory; Groth-Marnat, 2000). Similarly, patients are also instructed to restate the content of something they read in their own words in order to improve recall of these details (Kreutzer & Wehman, 1991). Other external aids typically employed include checklists, medication organizers, cue cards, post-it notes, and involving caregivers or loved ones in helping patients complete desired tasks (Groth-Marnat, 2000). However, as Groth-Marnat (2000) points out, the clinician must determine which strategies a patient is willing to use, and which are available to that patient (e.g., strategies requiring the reliance upon a caretaker are of little use to an individual caring for oneself).

Additional options open to treatment providers include prescribing stimulant or other drugs thought to improve cognition. However, studies examining the effect of drugs on the cognitive skills of MS patients show mixed results. For instance, a pilot study on the effects of l-amphetamine on cognitive impairment found improvements in working memory and processing speed, but no significant effect on memory (Benedict et al., 2008). In contrast, a larger, multi-site follow-up study found no significant effects of l-amphetamine on working memory and processing speed, the primary outcome measures; however, promising results were observed on secondary outcome measures of learning and delayed recall (Morrow et al., 2009). Memantine has shown no significant effect on cognitive performance in a similarly designed trial (Lovera et al., 2010), and its safety for use in MS has been questioned (Villoslada, Arrondo, Sepulcre, Alegre, & Artieda, 2009). Similarly, a study found that amantadine did not have a significant effect on cognitive test performance in MS (Geisler et al., 1996). Acetylcholinesterase inhibitors have shown some mixed success in producing objective improvements in neuropsychological outcomes in smaller pilot studies (Krupp et al., 2004; Krupp et al., 2010). However, a large multi-site trial of an acetylcholinesterase inhibitor found no benefit for cognitive difficulties in MS (Krupp et al., 2011). A small study that examined the effect of a single dose of armodafinil on cognition in MS found an improvement on a delayed verbal memory task, but not in other skills (Bruce, Hancock, Arnett, & Lynch, 2010). In summary, no effective drug treatment has yet been established for the treatment of cognitive deficits in MS. Despite the use of disease-modifying therapies and other drugs to combat cognitive decline in MS, there is a growing trend in the field to utilize cognitive rehabilitation techniques to ameliorate cognitive deficits.

Cognitive Training

Cognitive training is a process that is intended to strengthen cognitive skills, including attention, memory, problem-solving, and other executive functions. It is possible to improve or strengthen these skills because of plasticity, or the ability of the brain to reorganize its structure, functionality, and the connections between neurons (Cramer et al., 2011; Kolb et al., 2010). Injury to an area of the brain does not necessarily result in a permanent insult or skill deficit, as the brain sometimes has the ability to compensate for injuries and improve in functioning over time.

Cognitive Training in Normal Controls and Non-MS Patient Groups

Researchers have found some success in training both information processing speed and working memory in normal populations. Information processing speed is not isolated for cognitive training in normal populations often, but has been successfully improved in children (Mackey et al., 2011). Working memory has been successfully improved in a variety of different settings and with both children (Holmes et al., 2009; Mezzacappa & Buckner, 2010; Thorell, Lindqvist, Nutley, Bohlin, & Klingberg, 2009) and adults (Olesen, Westerberg, & Klingberg, 2004). Takeuchi and colleagues (2010) also found that training of working memory improved structural connectivity in regions of the brain thought to be important in working memory. Additionally, researchers have had success in the transfer of working memory training to other measurable skills, including fluid intelligence (Jaeggi et al., 2008; Jaeggi et al., 2010). These results suggest that skills targeted during cognitive training can generalize to improve other areas of cognition, rather than serving solely to strengthen the targeted domain.

Several research groups have attempted to achieve success in improving cognitive deficits in other populations, such as older adults, individuals with mild cognitive impairment, childhood cancer survivors, and people with schizophrenia (Berry et al., 2010; Hardy, Willard, & Bonner, 2011; Sartory, Zorn, Groetzinger, & Windgassen, 2005). Many of these studies have methodological flaws that could confound the findings. For instance, some use training programs that cover many skills superficially (Hardy et al., 2011), require only a minimal dose of training (Jean et al., 2010), or compare active training to an inactive control group (Berry et al., 2010; Bherer et al., 2008; Engvig et al., 2010; Sartory et al., 2005). Some studies employ a design whereby investigators who assess participants before and after training are not blind to treatment group (Couillet et al., 2010; Uchida & Kawashima, 2008). Moreover, the exact details of the cognitive training program employed in a study are often omitted, which creates problems both with replication and in evaluating whether the methods of training and measurement are truly distinct (Duff et al., 2010; Klingberg, Forssberg, & Westerberg, 2002).

In both normal and other populations, some studies fail to report data on adherence to the cognitive training program (Berry et al., 2010; Klingberg et al., 2002). Still other studies fail to comment directly on adherence to the training, but conducted training sessions in-person with their participants (Bherer et al., 2008; Couillet et al., 2010; Engvig et al., 2010; Mozolic et al., 2010; Sartory et al., 2005; Uchida & Kawashima, 2008), leaving questions about whether data from these studies could be artificially inflated by demand characteristics. Without data on how participants adhere to any cognitive training program, it is difficult to ascertain the true effects of the training plan. Perhaps some of these mixed findings are the result of partial adherence to the plan, meaning that participants were only partially trained to the targeted skills.

Despite their shortcomings, attempts to utilize cognitive training to bolster cognitive skills in various non-MS groups have shown promise. These studies overcame common methodological flaws chiefly by training to specific skills (Barnes et al., 2009; Edwards et al., 2005; Vance et al., 2007; Wadley et al., 2006), but also required a sufficient dose of training, (Barnes et al., 2009), and included an active/sham control group (Barnes et al., 2009; Edwards et al., 2005; Vance et al., 2007). Results from these studies support the construct of brain plasticity and the validity of engaging in cognitive training to improve skills in neurologic populations.

Cognitive Training in MS

Several researchers have focused on the application of cognitive training in MS (Brenk, Laun, & Haase, 2008; Hildebrandt et al., 2007; Jønsson et al., 1993; Mattioli et al., 2010; Plohmann et al., 1998; Shatil, Metzer, Horvitz, & Miller, 2010; & Solari et al., 2004; Tesar, Bandion, & Baumhackl, 2005; Vogt et al., 2009). Unfortunately, cognitive training programs implemented with MS patients have also shown inconsistent results, which has largely been attributed to methodological concerns (discussed later; O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008). Regardless, some of the findings from these studies show promise and indicate that further research on the topic is needed.

Most published studies in cognitive training with MS patients find modest improvements in at least some cognitive skills following training (see Brenk et al., 2008; Hildebrand et al., 2007; Jønsson et al., 1993; Plohmann et al., 1998; Shatil, et al,, 2010;

Solari et al., 2004; Tesar et al., 2005; Vogt et al., 2009). For instance, Brenk and colleagues (2008) examined cognitive training over a 6-week period that took place in participants' homes. Both MS patients and age-, gender-, and IQ-matched controls without MS were assessed at baseline and following training using neuropsychological outcome measures. Results indicated that differences after training were strongest in the areas of visuoconstructive ability and figural long-term memory.

Additionally, Hildebrandt and colleagues (2007) examined a home-based 6-week cognitive training program focused on memory and working memory, using a randomized controlled design with a MS patient comparison group which did not receive training. Results indicated that training had no effect on quality of life or fatigue, but the training group did show better verbal learning, long-delay verbal memory performance, and working memory performance. A different study examining a home-based computerized cognitive training program in an active training group and no training control group found improvements in overall memory, visual working memory, and verbal working memory (Shatil et al., 2010). Solari and colleagues (2004), however, found only one significant difference between their intervention and control groups following 8-weeks of cognitive training, on a word generation task. In summary, this body of research is clearly promising, as it shows some tangible results for cognitive problems faced by MS patients. However, the widely discrepant findings raise concerns about their application to these real-world problems. In other words, findings to date show limited generalizability and clinical application. Discrepancies in this research need to be identified and resolved in order for MS patients to receive maximum benefit from cognitive training.

Methodological Limitations of the Current Cognitive Training Literature in MS

As O'Brien and colleagues described in their 2008 review article, many of the studies focusing on training cognitive skills in MS suffer serious methodological flaws. Chief among these flaws is that recent work in the field has suggested that perhaps slowed information processing speed and impaired working memory are core cognitive deficits in MS (Bodling, Denney, & Lynch, 2008; D'Esposito et al., 1996; Denney, Lynch, & Parmenter, 2008; DeLuca et al., 2004; Reicker, Tombaugh, Walker, & Freedman, 2007). Yet, no cognitive training studies in MS have attempted to focus on improving information processing speed to date.

Problems with Training Protocols

Table 1 provides a comprehensive list of additional methodological problems found in cognitive training studies in MS. Studies that have found limited effects employ a blanket-style training protocol that covers many cognitive domains, but only superficially. For example, Jønsson (1993) and Shatil (2010) employed this approach and focused on multiple cognitive skills, including memory, visual perception, attention, and executive functions, rather than focusing on one or two core skills. In this type of program, each skill receives little attention because the total training time is divided among many skills. Also, some studies fail to mention whether the investigator who conducted the assessments was blind to treatment condition (Brenk et al., 2008; Plohmann et al., 1998; Shatil et al., 2010; Tesar et al., 2005; Vogt et al., 2009), and one reported that assessors were not blind to condition (Jønsson et al., 1993).

Finally, some make use of training that is poorly described and leaves the reader wondering whether it resembles the neuropsychological assessment tools used to measure cognitive deficit in the same study (Brenk et al., 2008; Hildebrandt et al., 2007; Mattioli et al., 2010; Shatil et al., 2010; Tesar et al., 2005). For example, Shatil and colleagues (2010) only state the name of the program, the number of tasks it presented to participants, and that these tasks cover a wide variety of cognitive skills. Additionally, Tesar and colleagues (2005) only vaguely describe their intervention as teaching compensation strategies. However, the reader is left not knowing whether these compensation strategies were taught as part of the commercial computerized program they employed, or whether they were taught in-person by a research assistant. As O'Brien and colleagues (2008) noted in their comprehensive review article, failure to adequately describe the intervention makes it exceedingly difficult for other researchers to replicate methodology. This is problematic because, even if investigators use commercially-available programs, the exact way in which the program was implemented with their participants needs to be stated clearly so replication and validation of findings can occur.

Problems with Control Groups

Another important methodological flaw relates specifically to the control groups included in these studies. Some researchers choose to utilize healthy controls rather than MS patients in a control group (Brenk et al., 2008), or a wait-list or inactive control group rather than assigning similar training tasks to controls (Hildebrandt et al., 2007; Shatil et al., 2010; Vogt et al., 2009). For instance, Brenk and colleagues (2008) utilized a healthy control group that was age-, gender-, and IQ-matched to their MS patients for comparison in their study. This is problematic because MS patients have very unique cognitive deficits, and the utility of comparing cognitive performance changes in a MS group compared to a healthy group is quite limited. Moreover, cognitive deficits in individuals with relapsing-remitting

Table 1

Common Methodological Problems among Cognitive Training Studies in MS

Methodological Problem	Study(ies) Containing this Problem
Inactive control group	Hildebrandt et al., 2007; Shatil et al., 2010; Vogt et al., 2009
Healthy control group	Brenk et al., 2008
Insufficient dose of training	Solari et al., 2004
Non-commercial training products	Hildebrandt et al., 2007; Plohmann et al., 1998; Shatil et al., 2010; Solari et al., 2004
Training too diffuse	Jønsson et al., 1993; Shatil et al., 2010
Training not described sufficiently to allow replication	Brenk et al., 2008; Hildebrandt et al., 2007; Mattioli et al., 2010; Shatil et al., 2010; Tesar et al., 2005
Training reliant upon clinic staff and resources	Mattioli et al., 2010; Solari et al., 2004
No data reported on training adherence	Hildebrandt et al., 2007; Tesar et al., 2005
Use of alternate forms of tests unclear	Mattioli et al., 2010; Plohmann et al., 1998; Shatil et al., 2010; Tesar et al., 2005; Vogt et al., 2009

MS can be present and then abate (O'Brien et al., 2008). Comparing this unique phenomenon to healthy individuals who will show very little to no variation in cognitive functioning from one time point to another has limited usefulness to researchers in this field. Additionally, two groups of investigators conducted a study whereby their training group of MS patients engaged in an extensive protocol, while controls received no training (Hildebrandt et al., 2007; Shatil et al., 2010). The promising results in these studies are confounded by the placebo effect, or the inability to determine whether actively engaging in a task believed to improve cognition contributed in some way to the outcome.

Other Methodological Flaws

Additional methodological problems include utilization of training that is often too brief (90 minutes per week; Solari et al., 2004). Moreover, the training programs employed often do not appear to easily translate into the clinical setting (Mattioli et al., 2010; Solari et al., 2004). For instance, one study utilized programs whereby patients travel to a clinic to meet in small groups led by a research assistant, and engage in training in a computer lab setting (Solari et al., 2004). Another study employed training conducted on an individual basis by a clinical neuropsychologist (Mattioli et al., 2010). This design limits the translation of cognitive training programs into the real world for MS patients. Many clinics would have difficulty providing this service to their patients, due to concerns related to ongoing expense, space, and billing. Many studies also utilize a training program produced by a third party, but these programs are not always widely available (Hildebrandt et al., 2007; Plohmann et al., 1998; Shatil et al., 2010; Solari et al. 2004). The advantages of at-home training (e.g., can be conducted at any time, does not require clinic staff) are lessened if the training programs are not widely available to those who need them. Furthermore, some studies fail to mention whether they employ the use of alternate forms when repeatedly administering neuropsychological assessment tools (Mattioli et al., 2010; Plohmann et al., 1998; Shatil et al., 2010; Tesar et al., 2005; Vogt et al., 2009). In these studies, the contribution of practice effects to the results cannot be ascertained.

An additional major oversight in this literature appears to be in that few of these studies have recorded and reported any objective adherence data (e.g., number of days per week they were engaged in training, and number of minutes per session). For instance, several of the studies in this small body of literature have failed to report any data on adherence to the intervention (Brenk et al., 2008; Hildebrandt et al., 2007; Jønsson et al., 1993; Mattioli et al., 2010; Plohmann et al., 1998; Tesar et al., 2005). As previously mentioned, determining the full effect of a training program is difficult when the reader is unsure whether participants fully engaged in training. Additionally, this is an important oversight if adherence to a cognitive training program is related to other types of treatment adherence. Studies examining medication adherence in MS showed that patients tend to over-report their adherence (Bruce et al., 2010). Therefore, it would not be surprising to find mixed results from cognitive training programs if these programs are not being fully adhered to by the participants.

Ideally, research in cognitive training will employ an intervention that is not only accessible but also produces tangible, replicable results. Therefore, designing a cognitive training study that targets the specific deficits believed to be most important in a particular population, is available to all members of that population, and can be validated using neuropsychological assessment tools is imperative.

Advancing Methodology to Improve Outcomes

Implementation of successful cognitive training programs in MS has the potential to improve overall quality of life, including treatment adherence, employment, and social relationships. Despite this, no published studies have attempted to overcome common methodological flaws when treating cognitive impairment in MS. The present study sought to improve the current literature on cognitive training in MS by implementing several important methodological advances. This investigation focused specifically on training information processing speed and working memory, the most fundamental deficits for MS patients. Additionally, researchers implemented a randomized controlled trial, whereby the control group consisted of MS patients. The MS control group engaged in a sham training task so that investigators could control for time spent in front of the computer engaging in a similar task. Moreover, researchers used counterbalanced neuropsychological assessments that do not resemble the training tasks. Both participants and the investigator who conducted the pre- and post-training assessments were blind to treatment condition. Finally, objective data was collected to explore how adherent MS patients are to a home-based cognitive training program.

The present study examined how cognitive training impacts objective neuropsychological performance in MS. The primary aim of the study was to determine whether cognitive training ameliorates cognitive difficulties in MS as measured by objective neuropsychological tests. This investigation was a pilot study and as such, only a small number of participants were recruited. Researchers had several hypotheses about the potential outcomes of this study:

- The primary hypothesis was that that information processing speed and working memory training would be associated with improved performance on neuropsychological tests that measure these skills.
- We also hypothesized that information processing speed and working memory training would be associated with improved performance on neuropsychological tests that measure other, associated skills.

The secondary aim of the study was to determine whether the effects of cognitive training on outcome measures vary as a function of adherence to the cognitive training program.

- It was hypothesized that participants who were more adherent to the training program, as measured by time spent engaged in training, would show greater improvements on outcome measures.

CHAPTER 2

METHODOLOGY

Participants

Patients with MS were recruited from both a large MS specialty clinic at the University of Kansas Medical Center and from the Kansas City metropolitan community. As compensation for their participation, participants received $50 and a copy of the cognitive training program. Study funding was provided by the University of Kansas Endowment: Boelte Family Fund for Multiple Sclerosis. Eligibility criteria included: (a) no history of alcohol/drug abuse; (b) no nervous system disorder other than MS; (c) no sensory impairments that might interfere significantly with cognitive testing or training; (d) no developmental history of learning disability or attention-deficit/hyperactivity disorder; (e) no relapse and/or corticosteroid use within four weeks of initial assessment; (f) absence of severe physical/neurological impairment that would make testing or training insurmountable; (g) a working home computer with internet access; (h) between the ages of 18 and 60. Each patient was diagnosed as having MS based on established criteria (McDonald et al., 2001) by a board-certified neurologist.

Procedures

The investigation involved a blinded, placebo-controlled design. Participants were randomly assigned to one of two groups: active cognitive training or control. A block stratified randomization method was employed to ensure equal numbers of each MS subtype in each training group. The active training group was asked to complete a computerized cognitive training program that specifically aimed to improve information processing speed and working memory. The control group was asked to complete a computerized cognitive training program that is almost identical to the active training group, but this program does not aim to improve information processing speed or working memory. This latter program employed the same tasks as the former, but it does not increase in difficulty in order to challenge participants to improve.

Participants attended two appointments for neurocognitive testing: once at baseline prior to group assignment, and once after completion of the 6-week intervention (active training or control). These study appointments took place at the participants' location of choice: the University of Kansas Medical Center Landon Center on Aging, the University of Missouri-Kansas City Department of Psychology, or their own private residence. However, the location of study appointments was held constant for each participant across the study. The investigators who conducted the study appointments and testing were blind to the treatment condition. Additionally, participants were asked to complete several paper-and-pencil self-report measures at each of these appointments. Please see Figure 1 for a visual study timeline.

Measures

Cognitive Training

Active Training Group. Participants who were randomly assigned to this group engaged in computerized training in their homes using Posit Science InSight and BrainTwister Visual N-Back programs supplied by the researchers. The InSight product has shown some promise in its ability to train specific skills, and also in the transfer of skill from areas trained to areas not trained (Posit Science; Ball et al., 2007; Edwards et al., 2002; Smith et al., 2009). For instance, Smith and colleagues (2009) conducted a study whereby a large group of older adults engaged in 40 hours of training over 8 weeks and showed improvements in processing speed, overall memory, list learning, delayed recall, and working memory. Ball and colleagues (2007) combined data from six studies which utilized InSight and determined that speed of processing training in older adults improves not only performance on assessment tools (e.g., Useful Field of View Test), but also in everyday activities, such as safer driving and instrumental activities of daily living. Finally, Edwards and colleagues (2002) also found that speed of processing training results in improvements in older adults' ability to perform instrumental activities of daily living. However, the overwhelming majority of research using Posit Science products has been conducted in the older adult population. To the knowledge of the researchers, this product has never been applied in the MS population.

The BrainTwister software was first developed for research and is now available commercially (BrainTwister). One task contained within this package is a visual n-back task to train working memory (Jaeggi et al., 2007). A recent study by Jaeggi and colleagues (2010) found both measurable increases in working memory and fluid intelligence for healthy individuals who engaged in training with a single n-back task. Researchers have also demonstrated that working memory training results in improvements in tests which measure this skill in MS patients (Vogt et al., 2009).

The active training group completed only select modules from these commercially-available cognitive training packages. Specifically, participants completed two games that aimed to improve information processing speed (Sweep Seeker and Road Tour), and two games that aimed to improve working memory (Master Gardner and Visual N-Back). These tasks continually challenged participants and automatically increased level of difficulty once the previous level was mastered. Participants were asked to engage in training six days per week, for thirty minute intervals, for a six-week period. They spent three days per week engaged in information processing speed training, and three days per week engaged in working memory training. This specific schedule of training was determined based on several factors: 1) no dose effect has been established for cognitive training, so we looked to the literature to determine a suggested schedule; 2) many published studies on cognitive training use a similar schedule (e.g., Brenk et al., 2008 & Hildebrandt et al., 2007); and 3) we felt this schedule would be sufficiently long to produce change without being so long that it would reduce likelihood of completion. Individuals in this group received detailed instructions regarding which modules to complete and how to use the software. Additionally, they received contact information for a research assistant who could assist them with technical or logistical software problems as they engaged in the training process.

Control Group. Participants who were randomly assigned to this group participated in a sham training task with the same software given to the active training group. Participants were asked to engage in computerized training in their homes for the same time intervals as the active training group, which controls for type of task, time spent in front of the computer, and time spent engaging in a task thought to improve cognitive skills. Control group participants completed the same modules as the active training group participants (Sweep Seeker, Road Tour, Master Gardner, and Visual N-Back), but their tasks did not continue to grow more challenging. Participants were asked to engage in training six days per week, for thirty minute intervals, for a six-week period. They spent three days per week engaged in information processing speed training, and three days per week engaged in working memory training. Individuals in this group also received detailed instructions regarding which modules to complete and how to use the software. Additionally, they received contact information for a research assistant who could assist them with technical or logistical problems as they engaged in the training process.

Information Processing Speed Tasks. Two information processing speed tasks were employed in this study: Sweep Seeker and Road Tour. These tasks were presented in a game format with an associated story, in which participants earned points for their performance. In Sweep Seeker, participants were presented with a grid of tiles. Each tile contains a picture, and participants were asked to eliminate tiles one at a time from the grid so that groups of three or more tiles line up horizontally. The goal of grouping same tiles is to make those tiles disappear from the grid, which earns the participant points. Eliminating single tiles requires a participant to view and correctly identify two visual sweeps. Visual sweeps are groups of vertical lines oriented around a central vertical axis. The lines vary in thickness, speed, proximity to one another, and color. Participants had to correctly identify whether the lines were moving in (toward the vertical axis) or out (away from the vertical axis). Each trial contained two sweeps or movements. For the active training group, the game continually challenged participants by increasing the speed of the line movements, decreasing their thickness, and decreasing the distance between lines.

In Road Tour, participants played a game aimed at moving their white car around the periphery of the screen. Cars of varying color and type are aligned in a circle around the screen. The game is divided into small trials. In each, participants were presented simultaneously with the image of a car in the center of the screen, and the image of a Route 66 sign near the periphery. Next, participants were shown the images of two cars in the center of the screen and had to correctly identify which car was shown to them in the prior moment. After correct identification of the car, participants had to then correctly identify the section of the circle where the Route 66 sign was presented. Correct identification of this section allows participants to replace one of the cars in the circle for a different-colored car in order to form groups of at least three of the same color. The goal was to create groups of same-colored cars so that the participant's white car moved around the circle and earned points. For the active training group, duration of stimuli presentation gradually decreased to become more challenging.

Working Memory Tasks. Two working memory tasks were employed in this study: Posit Science's Master Gardener and the Brain Twister N-Back Task. In Master Gardener, participants played a game aimed at building a complete garden. The game displayed three different types of seed packets, one at a time, for a brief moment. Two are identical, and the participant must correctly identify the identical pair by clicking on the locations where they were displayed. Correct identification of the seed packet pairs causes flowers to grow in the chosen locations across the screen. For the active training group, the game continued to challenge participants by varying locations of the seed packets in their proximity to one another, increasing the number of possible seed packets to track, and decreasing the display time of the target stimuli (seed packets).

Finally, in the N-Back task, participants played a single-modality N-Back game. The paradigm is described in detail elsewhere (Jaeggi et al., 2007). In this study, only the visual modality was used. Participants were presented with a nine-position grid. A blue square appeared in the grid in a random sequence and utilized all but the center position on the grid. Participants were asked to remember the locations in which the square appeared, and pressed the spacebar when the square was in the same position as *n* steps back in the sequence (e.g., 2-back would be two steps back from the current position, 3-back is three steps back from the current position). The task provided on-screen directions indicating how many steps back to track. For the active training group, the task continually challenged participants by increasing the number of positions behind the current stimulus that they had to remember. For the control training group, the task was a 0-back condition, whereby participants responded to a pre-specified location rather than recalling any part of the sequence. The control N-Back task was created specifically for this study, but was modeled after the active group task.

Cognitive training progress reports. Each program utilized by participants in this study had the ability to store reports of training sessions. Participants were asked to e-mail these progress reports at least once per week, or more often if they chose. Detailed instructions regarding how to e-mail these reports were supplied to participants. The progress reports served as an objective measure of training program adherence. The variable of interest is the percentage of completed training sessions.

Cognitive training adherence diary. Each participant was provided with a calendar-style diary in which they were asked to record the date, time, and length of each training session over the six week period. The variable of interest is the percentage of completed training sessions.

Neurocognitive Functioning Battery

Investigators assessed neuropsychological functioning with a short battery that assessed key cognitive functions, including information processing speed, working memory, attention, memory, and learning. This battery was given at both baseline and follow-up testing. The tests do not resemble the cognitive training tasks. Most of the following tasks have equivalent alternate forms that were employed in a counterbalanced manner to minimize order and practice effects. A list of all measures administered can be found in Appendix A.

Paced Auditory Serial Addition Task. The Paced Auditory Serial Addition Task (PASAT) is a commonly used measure of speed of information processing in MS (Gronwall, 1977). It requires participants to quickly add consecutive numbers that are presented orally. This test is also part of the Multiple Sclerosis Functional Composite, described below (Cutter et al., 1999). The variable of interest was the combined total number of correct additions made in both the three-second and two-section versions. Equivalent alternate forms were used for this study.

Multiple Sclerosis Functional Composite. The Multiple Sclerosis Functional Composite (MSFC) is a small battery of tests that measure overall disability in MS (Cutter et al., 1999). Information processing speed, motor ability, and mobility are measured and combine to create an overall composite score. The test consists of the PASAT, 9-Hole Peg Test, and a Timed 25-Foot Walk. The primary variable of interest was the total composite score, with higher scores indicating greater disability.

Symbol Digit Modalities Test, Oral Version. The Symbol Digit Modalities Test (SDMT) is a measure of speed of information processing and selective attention that is commonly used in MS (Smith, 1982; Strauss, 2006). Participants were asked to quickly say numbers that match corresponding symbols by using a provided key. Scores on the SDMT have been shown to be related to neuroimaging indices of disease, including overall atrophy in MS patients (Christodoulou, Krupp, & Liang, 2003). The variable of interest was the total number of correct answers given in 90 seconds.

Stroop Test. The Stroop Test (Stroop, 1935) is a test of information processing speed and executive functioning that requires participants to inhibit a natural response (reading a word) and replace it with another response (saying a color). This study employed a computerized version of the classic task that included all three trials: word reading, color naming, and Stroop word naming. This task has been described in detail elsewhere, and has been validated for use with MS patients (Denney et al., 2011). Slower performance by MS patients on this task has been shown to be due to slowed information processing speed, not slowed reaction time or problems in executive functioning (Macniven et al., 2008). The variables of interest are the total number of correct responses and the total number of errors made during each trial.

Auditory Verbal Learning Test. The Auditory Verbal Learning Test (AVLT) is a test of verbal memory during which a person is asked to learn and recall a list of 15 unrelated words (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). This study employed alternate forms of the word list to reduce practice effects. The variant employed for this study included five learning trials and a delayed recall trial. The variables of interest were immediate word span, total learning, and delayed recall.

Conner's Continuous Performance Test-II. The Conners' Continuous Performance Test-II (CPT-II) is a test of sustained attention and response inhibition that has negligible practice effects (Conners, 2004; Strauss, 2006). In this computerized task, individuals are instructed to press the spacebar each time a letter is presented, other than the letter "X." The primary variable of interest was a standardized score of inattention.

Controlled Oral Word Associations Task. The Controlled Oral Word Associations Task (COWAT) is a test of verbal fluency in which a person is given a letter and asked to generate as many words as possible in 60 seconds (Stern & White, 2003; Strauss, 2006). This task contains three trials, with one letter per trial. Two versions of this task (using the letters FAS and BDT) have been found to show only minimal practice effects and adequate reliability (.72; Dikmen, Heaton, Grant, & Temkin, 1999). The variable of interest was the number of words generated within the time limit.

Computerized Assessment of Response Bias. The Computerized Assessment of Response Bias (CARB) is a measure of effort (Allen, Conder, Green, & Cox, 1997). Participants complete a forced-choice digit recognition procedure in which they first view a multi-digit number and then have to identify this number from a group of two after a short delay (Lezak et al., 2004). The variable of interest was the percentage of correct responses. If participants scored below a pre-established cut-point on this measure, those data were excluded from analyses.

Brief Visuospatial Memory Test. The Brief Visuospatial Memory Test (BVMT) is a test of visual memory during which a person is asked to learn and draw a series of abstract designs (Benedict et al., 1996). The BVMT has several alternate forms that have been deemed equivalent to use in order to reduce practice effects. The primary variable of interest was the total score, which is derived from both construction and placement of each figure.

Raven's Advanced Progressive Matrices. The Advanced Progressive Matrices (APM) is a test of fluid intelligence (Raven, Raven, & Court, 1998). Participants were asked to view a pattern, with one piece of the pattern missing. The task was to correctly identify the missing piece from several options provided by inferring the rule used to create the pattern (Alderton & Larson, 1990). Though no alternate forms of this test exist, previous researchers have established that the split-half reliability of the task is strong and split-halves have been employed in a similar paradigm to this study's (.83-.87; Bors & Stokes, 1998; Jaeggi et al., 2008; Raven et al., 1998). Split-half versions of the task were administered in a counterbalanced fashion for this study. The primary variable of interest was number of correct answers given.

Letter-Number Sequencing. The Letter-Number Sequencing (LNS) task is a test of working memory. Participants were asked to listen to a mixed sequence of letters and numbers, and then repeat the sequence back to the examiners with the numbers in numerical order and letters in alphabetical order (Wechsler, 1997). Alternate forms of this task are not available, though there is evidence to suggest that scores on LNS remain stable over repeated administration (Beglinger et al., 2005). The primary variable of interest was the total number of correct sequences given.

Digits Backward. Digits backward is a test of working memory. Participants were asked to listen to a series of numbers, and then repeat the sequence back to the examiner in reverse order. (Stern & White, 2003). The test has alternate forms that have been deemed equivalent to use in order to reduce practice effects. The variable of interest was the total number of correct sequences given.

Wechsler Test of Adult Reading. The Wechsler Test of Adult Reading (WTAR) is a reading test in which participants are asked to pronounce irregularly spelled words aloud (Strauss, 2006; Wechsler, 2001). This test was administered only once in this study. The primary variable of interest was the raw score. This test was included in the baseline battery so that investigators could adequately describe the overall cognitive functioning of the sample and use intellectual functioning as a covariate in statistical analyses if necessary.

Psychological Functioning

A list of all measures administered can be found in Appendix B.

Beck Depression Inventory – Fast Screen. The Beck Depression Inventory – Fast Screen (BDI) is a self-report questionnaire designed to quickly assess common symptoms of depression (Beck, Steer, & Brown, 2000). It contains seven items designed specifically to assess depression in a medical population. This measure was included so investigators could examine whether depression is related to adherence to the training intervention, and use depression as a covariate in statistical analyses if necessary. The primary variable of interest was the total score, with higher scores indicating more depression.

State-Trait Anxiety Inventory. The State-Trait Anxiety Inventory (STAI) is a 40-item self-report measure designed to assess both state and trait anxiety (Spielberger, 1983). This measure was included so investigators could examine whether state or trait anxiety is related to adherence to the training intervention, and use state or trait anxiety as a covariate in statistical analyses if necessary. The primary variables of interest were the total score on the state subscale and total score on the trait subscale, with higher scores indicating more anxiety.

Other Self-Reported Functioning

Multiple Sclerosis Quality of Life. The Multiple Sclerosis Quality of Life (MS-QOL) is a multi-dimensional self-report questionnaire designed to assess health-related quality of life in MS (Vickrey, 1995). The questionnaire contains 54 items that tap a variety of issues including pain, general health, and sexual functioning. This questionnaire was included in the baseline battery so that investigators could adequately describe the overall functioning of the sample as it relates specifically to MS patients, and use self-reported quality of life as a covariate in statistical analyses if necessary. The primary variable of interest was the total score, with higher scores indicating greater distress in quality of life.

Modified Fatigue Impact Scale. The Modified Fatigue Impact Scale (MFIS) is a 21-item self-report measure designed to assess cognitive, physical, and social fatigue in MS (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994). This measure was included because fatigue is a common phenomenon in MS and has been linked to performance on cognitive measures (Benedict et al., 2005; Bol et al., 2010; Branas et al., 2000; Bruce, Bruce, & Arnett, 2010). The inclusion of this measure allowed investigators to examine whether fatigue changed as a result of the intervention, or use it as a covariate in statistical analyses if necessary. The primary variable of interest was the total score, with higher scores indicating more perceived fatigue.

Computer Use Questionnaire. The Computer Use Questionnaire is a brief self-report measure designed to assess perceived comfort with using a computer. This measure was included so investigators could examine greater computer use as a covariate in statistical analyses if necessary. The primary variable of interest was the total number of hours engaged in using a computer for any reason in an average week.

Satisfaction Survey. The Satisfaction Survey is a brief self-report measure designed to assess perceptions about different aspects of the study. This measure was included so investigators could examine participant reactions to the training schedule, training tasks, and overall feasibility of the protocol.

Data Analysis

Analyses were conducted using SPSS 20. First, independent samples t- tests were used to compare both groups at baseline measurements. We used a Bonferroni correction to conservatively control for familywise error. If analyses reveal that the two groups were not equivalent at baseline, we employed statistical covariates in order to control for inequality. Next, we conducted hypothesis testing. There were three hypotheses to be tested in this study. First, it was hypothesized that information processing speed and working memory training would be associated with improved performance on separate neuropsychological tests that measure these skills. Second, it was hypothesized that information processing speed and working memory training would be associated with improved performance on neuropsychological tests that measure other, associated skills. To analyze the effect of training on outcome measures, a 2 x 2 mixed-factor Analysis of Variance (ANOVA) was employed, including a within-subject factor of test performance over time (pre- vs. post-training) and a between-subjects factor of group (active training vs. control). We chose to utilize multiple ANOVA analyses rather than multivariate analysis of variance (MANOVA) because we wanted to be able to determine the effect of training on individual neuropsychological constructs. We felt that using ANOVAs would allow us to better appreciate the relative effects of training on different measures. We once again employed Bonferroni correction to conservatively control for familywise error. Finally, it was hypothesized that participants who were more adherent to the training program would show greater improvements on outcome measures. To analyze the effect of adherence on outcome measures, correlations between adherence and percent change on outcome measures of interest were conducted.

Additionally, researchers planned some secondary analyses in order to explore the full effect of cognitive training in this pilot study. Measures of physical disability, intelligence, and self-reported computer use were used in order to ensure equality of the randomly assigned groups. Additionally, a measure of effort was included so that researchers could ensure that all participants were providing adequate effort during neuropsychological testing. These measures helped inform researchers as to whether data should be excluded from analyses. Finally, we also planned to report descriptive data on the satisfaction survey administered to participants, as this would help provide qualitative information regarding the feasibility of computer-based cognitive training in MS patients.

We utilized adherence data to determine how many participants followed the training schedule. A priori, we set a threshold of 80% adherence to training schedule to be considered adherent. We analyzed whether any significant findings were still present when we examined only good adherers. We also analyzed any possible effect of training on self-reported depression, anxiety, fatigue, or quality of life. In order to analyze these effects, a 2 x 2 mixed-factor (ANOVA) was employed, including a within-subject factor of test performance over time (pre- vs. post-training) and a between-subjects factor of group (active training vs. control).

Finally, if improvements in neuropsychological outcome measures were shown, we planned to follow-up those analyses with calculations of a reliable change index (RCI). Recently, researchers in the area of intervention have made strong arguments for the importance of determining whether change that is detected statistically can be considered significant at the individual level (Hinton-Bayre, 2010; Maassen, Bossema, & Brand, 2009). The RCI allows for an assessment of the magnitude of change of scores for an individual that are not susceptible to group means and standard deviations. This process has been described in detail elsewhere (Hinton-Bayre, 2010; Maassen, Bossema, & Brand, 2009). We used the

Jacobson-Truax method and use a 0.90 confidence interval, which indicates a 95% chance of true improvement for anyone who passes the threshold (Jacobson & Truax, 1991).

CHAPTER 3

RESULTS

Preliminary Analyses

Seventy-one participants with MS completed the baseline assessment. There was significant attrition from the study, as 31 participants either withdrew from the study or were lost to follow-up. Analyses indicated that there were no significant differences between the participants who completed the study compared to those who did not in age, education, frequency of computer use, intellectual functioning, MSFC score, disease duration, anxiety, depression, or fatigue. Reasons for withdrawal include work demands (30%), not being able to do the training consistently (25%), family demands (25%), and loss to follow-up (20%). Figure 2 depicts the recruitment process for this study.

The final sample included 40 individuals with MS who were predominantly female (87.5 %). The sample was mostly European-American (90 %) with some African-Americans (7.5 %) and Hispanic-Americans (2.5 %). The majority of participants were diagnosed with relapsing-remitting subtype (70 %), with some secondary-progressive (18 %), primary-progressive (10 %), and progressive-relapsing (2 %). The mean ± *SD* age of participants was 48.80 ± 9.18 years with 15.45 ± 2.53 years of education. Disease duration was 146.92 ± 82.66 months with a mean MSFC score of -0.08 ± 0.63. On average, participants reported they used a computer 2.78 ± 1.31 hours per week. All participants passed effort testing and therefore did not need to be excluded from analyses.

After random assignment, the groups had the following characteristics. Twenty participants were randomized to the Active Training group, which was predominantly female (90%) and European-American (85%), with some African-Americans (10%) and one

Hispanic-American (5%). The majority was diagnosed with relapsing-remitting MS (65%), with some secondary-progressive (15%), primary-progressive (15%), and one progressive-relapsing (5%). The mean ± *SD* age of participants in the Active Training group was 48.45 ± 8.10 years with 14.60 ± 1.95 years of education. Disease duration was 126.75 ± 65.25 months with a mean MSFC score of -0.066 ± 0.69. On average, participants in this group reported they used a computer 2.75 ± 1.37 hours per week.

Twenty participants were randomized to the Sham Training group, which was also predominantly female (85%) and European-American (95%), with one African-American (5%). The majority was diagnosed with relapsing-remitting MS (75%), with some secondary-progressive (20%), and one primary-progressive (5%). The mean ± *SD* age of participants in the Sham Training group was 49.15 ± 10.41 years with 16.30 ± 2.79 years of education. Disease duration was 167.10 ± 94.40 months with a mean Multiple Sclerosis Functional Composite (MSFC) score of -0.095 ± 0.59. On average, participants in this group reported they used a computer 2.80 ± 1.28 hours per week. Analyses indicated that age and baseline MSFC scores did not significantly differ between groups, but education did (t (38) = 2.23, p = .032). As a result, education was included as a covariate in hypothesis testing analyses. Additional descriptive information can be found in Table 2. Importantly, participants in the two groups did not differ in their scores on neuropsychological outcome measures at baseline. These data can be found in Table 3.

Regarding adherence, participants in both groups were asked to engage in training for six thirty-minute sessions per week for six weeks. In a given training day, participants trained using two tasks for approximately 15 minutes each. In total, participants were asked to engage in 810 minutes of training (four tasks for 18 sessions, approximately 270 minutes each). Percentage of training completed was calculated by comparing the reported number of minutes engaged in training to the total expected based on the study requirements. We collected adherence data by two methods: computer generated reports sent to researchers by participants (deemed objective adherence data) and by a self-report calendar-style diary (deemed self-report adherence data).

Objective adherence data was reported by 75% of participants. Specifically, 70% of the Sham Training group and 80% of the Active Training group provided objective adherence data. Self-reported adherence data was available for 85% of participants. Specifically, 85% of each group's participants supplied these data. The majority of participants reported they perfectly adhered to the training schedule, regardless of group assignment. In the Active Training group, 63% reported perfect objective adherence and 59% reported the same via the adherence diary. In the Sham Training group, 71% reported perfect objective adherence and 59% reported the same via the adherence diary. Between objective and self-reported methods, we were able to collect adherence information for each participant who completed the study. Importantly, adherence rates in the two groups were not significantly different for objectively reported adherence (t (28) = 0.148, p = 0.883) or self-reported adherence (t (32) = 0.605, p = 0.549).

Table 2

Participant Demographics by Group

	Active Training Group		Sham Training Group		t-test
Characteristic	Mean	*SD*	Mean	*SD*	*p*
Age (years)	48.45	8.01	49.15	10.41	0.81
Education (years)	14.60	1.96	16.30	2.79	0.03
Disease duration (months)	126.75	65.25	167.10	94.40	0.12
STAI – State Anxiety	46.15	5.08	43.65	6.62	0.18
STAI – Trait Anxiety	45.20	4.55	43.72	5.91	0.39
BDI-FS	4.42	2.80	3.30	3.45	0.27
MSFC score	-0.07	0.69	-0.10	0.59	0.89
WTAR	35.10	8.85	39.05	7.89	0.14
Computer use per week (hours)	2.75	1.37	2.80	1.28	0.91

Note. Values at baseline. STAI = State Trait Anxiety Inventory, BDI-FS = Beck Depression Inventory – Fast Screen, MSFC = Multiple Sclerosis Functional Composite, WTAR = Wechsler Test of Adult Reading. *N* = 40.

Table 3

Scores on Neuropsychological Outcome Measures at Baseline

	Active Training Group		Sham Training Group		t-test		
Variable	Mean	*SD*	Mean	*SD*	*t*	df	*p*
PASAT	76.95	18.47	74.61	24.64	-0.328	35	0.745
SDMT	48.45	11.20	49.15	16.72	0.156	38	0.877
Stroop	33.00	6.94	31.10	8.32	-0.784	38	0.438
LNS	10.15	2.35	10.70	3.20	0.620	38	0.539
Digits Backward	4.95	1.88	4.80	1.82	-0.256	38	0.799
Raven's	8.60	4.16	9.00	4.41	0.295	38	0.770
BVMT	18.10	4.84	18.63	7.09	0.275	37	0.785
COWAT	37.10	9.68	39.50	15.54	0.586	38	0.561
CPT	53.77	8.84	50.01	11.91	-1.126	37	0.267
AVLT	48.05	9.42	42.30	9.63	-1.909	38	0.064

Note. PASAT = Paced Auditory Serial Addition Test, SDMT = Symbol Digit Modalities Test, LNS = Letter-Number Sequencing, BVMT = Brief Visuospatial Memory Test Trials 1-3, COWAT = Controlled Oral Word Associations Task, CPT = Conner's Continuous Performance Task Commissions, AVLT = Auditory Verbal Learning Task Trials 1-5. $N = 40$.

Hypothesis Testing

Table 4 shows descriptive statistics for all of the variables of interest at both baseline and follow-up testing sessions. First, it was hypothesized that information processing speed and working memory training would be associated with improved performance on separate neuropsychological tests that measure these skills. The only significant difference in measures of information processing speed and working memory was an interaction between group and time in the PASAT (F = 10.30, partial eta^2 = 0.232, p = 0.003). The effect remained significant after we applied the Bonferroni correction. A within-subjects analysis confirmed that there was significant improvement in the PASAT scores across time (t (18) = -4.44, p = 0.000) in the Active Training group. By contrast, in the Sham Training group, no difference was found for the PASAT across time (t (17) = -1.37, p = 0.189). The interaction between group and time in PASAT scores from baseline to follow-up assessment by group is depicted in Figure 4.

Second, it was hypothesized that information processing speed and working memory training would be associated with improved performance on neuropsychological tests that measure other, associated skills. The only significant difference in associated skills was in the interaction between group and time on the COWAT (F = 5.85, partial eta^2 = 0.137, p = 0.021). This effect did not remain significant when we applied the Bonferroni correction. Within-subjects analysis showed that there was a significant improvement in COWAT scores across time for the Active Training group (t (18) = -4.07, p = 0.001), but not the Sham Training group (t (19) = 0.983, p = 0.338).

Table 4

Analyses Depicting the Interaction Effect when Comparing Groups on Outcome Measures

	Active Training Group				Sham Training Group				GLM Interaction Effect				
	Baseline		Follow-up		Baseline		Follow-up						observed
Variable	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)	*F*	df	*p*	*eta*^{2}	power
Hypothesis 1: Information Processing Speed & Working Memory Skills													
PASAT	76.95	(18.47)	88.05	(21.59)	74.61	(24.64)	76.67	(22.40)	10.299	34	0.003	0.232	0.885
SDMT	48.45	(11.12)	50.85	(11.52)	49.15	(16.72)	50.50	(15.14)	0.689	37	0.412	0.018	0.128
Stroop	33.00	(6.94)	35.60	(7.52)	30.37	(7.86)	32.16	(7.54)	1.619	36	0.211	0.043	0.236
LNS	10.15	(2.35)	11.15	(2.39)	10.70	(3.20)	10.95	(2.91)	2.857	37	0.099	0.072	0.377
Digits Backward	4.95	(1.88)	5.05	(1.73)	4.80	(1.82)	5.10	(2.25)	0.009	37	0.925	0.000	0.051
Hypothesis 2: Associated Skills													
Raven's	8.84	(4.13)	9.32	(3.47)	9.31	(4.03)	10.44	(4.35)	0.119	32	0.732	0.004	0.063
BVMT	18.10	(4.84)	21.45	(4.87)	18.63	(7.09)	20.05	(6.81)	3.036	36	0.090	0.078	0.396
COWAT	37.10	(9.68)	42.15	(15.23)	39.50	(15.54)	37.95	(14.23)	5.850	37	0.021	0.137	0.654
CPT	53.06	(8.44)	48.00	(9.85)	50.81	(11.70)	49.50	(12.30)	3.774	33	0.061	0.103	0.471
AVLT	48.05	(9.42)	52.65	(9.55)	42.30	(9.63)	45.95	(11.49)	1.673	37	0.204	0.043	0.243

Note. Education included as a statistical covariate. Data are presented for interaction effects. PASAT = Paced Auditory Serial Addition Test, SDMT = Symbol Digit Modalities Test, LNS = Letter-Number Sequencing, BVMT = Brief Visuospatial Memory Test Trials 1-3, COWAT = Controlled Oral Word Associations Task, CPT = Conner's Continuous Performance Task Commissions, AVLT = Auditory Verbal Learning Task Trials 1-5. *N* = 40.

Finally, it was hypothesized that participants who were more adherent to the training program would show greater improvements on outcome measures. Analyses indicated a lack of variability in our adherence data. For all participants, the mean ± *SD* percentage of completed training (by objective report) was 94.63 ± 12.58 and 87.43 ± 19.19 percent of completed training (by self-report). For the Active Training group, the amount of completed training by objective report was 94.63 ± 12.58 percent and the amount of completed training by self-report was 87.43 ± 19.19 percent. For the Sham Training group, the amount of completed training by objective report was 95.30 ± 12.01 percent and the amount of completed training by self-report was 90.92 ± 14.02 percent. The modal amount of reported training was 100% for both objective and self-report methods. Histograms that give a visual depiction of the amount of completed training for each method of reporting (objective and self-report) for the total sample can be found in Figure 5. Due to the very small number of people who completed the training protocol and did not have acceptable adherence (n = 7), we decided to forgo these planned analyses.

Reliable Change Analyses

We computed a reliable change index score for the differences observed on the PASAT. The reliable change index allows researchers to determine whether changes in scores at the individual level are statistically significant. The formula accounts for the reliability of the measure, and how individual participants scored both before and after the intervention (Jacobson & Truax, 1991). The formula can be found in Appendix C. Calculating a reliable change index score involved subtracting the individual's baseline score on the measure of interest from their follow-up score, then dividing that value by the standard error of the difference of the measure of interest (Jacobson & Truax, 1991). Using this method, we computed a change score for each participant in the Active Training group on the PASAT. To achieve a 90% confidence interval, and individual score change of at least 12 points was required. A total of 10 of the participants in the Active Training group (53%) showed change that surpassed the threshold to be considered reliable change. By contrast, a total of one of the participants in the Sham Training group (5%) showed change that surpassed the threshold to be considered reliable. A Chi-Square test revealed that the difference between reliable changes in the two groups was significant (X^2 (1) = 8.10, p = 0.004).

Secondary Analyses

As planned, additional analyses were conducted in order to explore all of the possible effects of training. We analyzed whether scores on self-report measures of anxiety, depression, fatigue, or quality of life changed as a result of engaging in training. Changes in any of these scores were neither hypothesized nor expected, but we wanted to explore whether any of these factors may have contributed to the changes observed in the PASAT. No significant changes were found. These data can be found in Table 5.

It is worth noting some data that show a trend toward significance. We found a trend of improved scores in an additional task of targeted skills in the LNS (F = 2.86, partial eta^2 = 0.072, p = 0.099). We also found a trend of improved scores in two associated skills: the CPT (F = 3.77, partial eta^2 = 0.103, p = 0.061) and BVMT (F = 3.04, partial eta^2 = 0.078, p = 0.090).

We conducted additional analyses to determine if results were the same when we included only individuals who properly adhered to training. We determined a priori that adherence to the training schedule of at least 80% was required in order to accurately measure the effects of training. A decision tree depicting our process for determining which participants should be included in the final sample is shown in Figure 3. After eliminating individuals with no adherence data or poor adherence, the sample included 33 participants. Analyses indicated that age, education, and baseline MSFC scores did not significantly differ between groups. We conducted the same hypothesis testing analyses with just the participants who showed good adherence to the training schedule. Results remained the same. We found a significant interaction in scores on the PASAT (F = 10.184, partial eta^2 = 0.260, p = 0.003) in the Active Training group, even after applying a Bonferroni correction. Improvements in scores on the COWAT (F = 2.777, partial eta^2 = 0.082, p = 0.106) and BVMT (F = 2.408, partial eta^2 = 0.131, p = 0.074) showed a trend toward significance. Data from these analyses has been summarized in Table 6.

Table 5

Analyses Depicting the Interaction Effect when Comparing Groups on Self-Report Measures

	Active Training Group				Sham Training Group				GLM Interaction Effect				
	Baseline		Follow-up		Baseline		Follow-up						observed
Variable	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)	*F*	df	*p*	eta^2	power
STAI State	46.15	(5.08)	45.60	(6.29)	43.93	(7.41)	44.33	(5.73)	0.466	32	0.500	0.014	0.102
STAI Trait	44.72	(3.97)	45.50	(5.11)	43.57	(6.45)	44.64	(5.71)	0.018	29	0.894	0.001	0.052
BDI-FS	4.42	(2.80)	4.00	(2.79)	3.47	(3.68)	2.60	(2.47)	0.373	31	0.546	0.012	0.091
MFIS	45.60	(12.00)	43.95	(17.45)	51.80	(16.81)	43.60	(18.98)	0.822	32	0.371	0.025	0.142
MSQOL	66.75	(9.97)	70.50	(12.77)	71.33	(19.45)	75.45	(15.12)	0.373	32	0.546	0.012	0.091

Note. Education included as a statistical covariate. Data are presented for interaction effects. STAI = State-Trait Personality Inventory, BDI-FS = Beck Depression Inventory – Fast Screen, MFIS = Modified Fatigue Impact Scale, MSQOL = MS Quality of Life Questionnaire. $N = 40$.

Table 6

Analyses Depicting the Interaction Effect when Comparing Groups on Outcome Measures for Good Adherers

	Active Training Group				Sham Training Group				GLM Interaction Effect				
	Baseline		Follow-up		Baseline		Follow-up						observed
Variable	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)	Mean	(*SD*)	*F*	df	*p*	eta^2	power
Hypothesis 1: Information Processing Speed & Working Memory Skills													
PASAT	80.69	(17.09)	92.69	(16.70)	74.86	(26.44)	77.33	(24.23)	10.18	29	0.003	0.260	0.869
SDMT	49.53	(10.74)	52.00	(11.31)	48.87	(18.63)	49.94	(15.60)	0.364	31	0.551	0.012	0.090
Stroop	32.88	(7.33)	35.47	(8.19)	30.94	(8.11)	33.12	(6.71)	0.065	31	0.800	0.002	0.057
LNS	10.29	(2.49)	11.06	(2.36)	10.63	(2.87)	10.88	(3.12)	0.477	31	0.495	0.015	0.103
Digits Backward	4.94	(1.60)	4.88	(1.69)	4.88	(1.89)	5.44	(2.28)	1.162	31	0.289	0.036	0.181
Hypothesis 2: Associated Skills													
Raven's	9.31	(3.65)	9.06	(3.11)	9.50	(4.27)	11.07	(4.29)	1.604	28	0.216	0.054	0.231
BVMT	18.24	(4.44)	21.18	(4.65)	19.13	(6.69)	19.87	(6.80)	2.408	30	0.131	0.074	0.324
COWAT	37.82	(9.69)	42.94	(15.67)	39.38	(15.13)	39.88	(13.59)	2.777	31	0.106	0.082	0.365
CPT	51.99	(8.35)	48.27	(10.32)	51.80	(12.62)	50.63	(13.10)	1.080	29	0.307	0.036	0.171
AVLT	47.53	(8.88)	52.53	(9.00)	41.93	(10.32)	45.56	(12.33)	0.390	31	0.537	0.012	0.093

Note. Data are presented for interaction effects. PASAT = Paced Auditory Serial Addition Test, SDMT = Symbol Digit Modalities Test, LNS = Letter-Number Sequencing, BVMT = Brief Visuospatial Memory Test Trials 1-3, COWAT = Controlled Oral Word Associations Task, CPT = Conner's Continuous Performance Task Commissions, AVLT = Auditory Verbal Learning Task Trials 1-5. *N* = 33.

Finally, we conducted analyses on the satisfaction survey. All participants who attended both study appointments completed this survey. We analyzed responses for all participants (those assigned to both groups) first, and then examined responses by group assignment. Importantly, the two groups did not differ in their responses to these questions. Participants were asked to rate their satisfaction with the overall study on a 4-point Likert scale, ranging from "not at all satisfied" to "very satisfied." 70% of all participants reported they were very satisfied with their overall experience in the study, with an additional 20% who reported they were mostly satisfied. Similarly, 61% of those in the Active Training group reported they were very satisfied with the overall study experience, with an additional 22% who reported they were mostly satisfied. Sham Training group participants also reported satisfaction to the overall study, with 83% reporting that they were very satisfied and an additional 17% reporting they were mostly satisfied. Participants were asked to rate their satisfaction with the overall cognitive training programs; the resulting data are illustrated in Figure 6. 53% of all participants reported they were very satisfied with the cognitive training programs, with an additional 40% who reported they were somewhat satisfied. Similarly, 56% of the participants in the Active Training group reported they were very satisfied with the cognitive training programs, with an additional 33% who reported they were somewhat satisfied. Finally, 50% of the participants in the Sham Training group reported that they were very satisfied with the cognitive training programs, with an additional 50% who reported they were somewhat satisfied.

We also asked participants to rate their satisfaction with the length of the individual training sessions (30 minutes each) and the length of the training program (6 weeks). A visual depiction of scores on each of these questions can be found in Figure 7 and Figure 8.

Once again, we analyzed responses for all participants and then by group. Satisfaction was rated on a 4-point Likert scale, ranging from “too short” to “much too long.” 71% of all participants rated the individual training sessions as “just right” in length, but 22% reported the sessions were “a little too long.” Among those in the Active Training group, 55% reported the individual sessions were “just right” in length, with 33% who reported the sessions were “a little too long.” For participants in the Sham Training group, 92% reported that the sessions were “just right” in length, with the remaining 8% who reported the sessions were “a little too long.” Regarding the length of the total training program, 68% reported the overall program to be “just right” in length, but 26% reported the overall program to be “a little too long.” For participants in the Active Training group, 56% reported the length of the overall program was “just right,” 33% reported it was “a little too long,” and 11% reported the program was “too short.” For participants in the Sham Training group, 85% reported the length of the overall program was “just right” and 15% reported it to be “a little too long.” Finally, participants overwhelmingly favored the Posit Science games over the BrainTwister task. 77% of all participants reported their preferred games were the Posit Science tasks, compared to 3% who reported their preferred task to be the N-Back task. For participants in the Active Training group, 72% reported their preferred games to be the Posit Science tasks, with just 5% who favored the BrainTwister N-Back. In the Sham Training group, 85% reported they preferred the Posit Science tasks and none reported that they preferred the Visual N-Back task.

CHAPTER 4

DISCUSSION

The results from this randomized, controlled, blinded pilot study of cognitive training in MS support the theory that select cognitive skills, as measured by neuropsychological tests, can be modestly improved in this population. Specifically, our study sought to target information processing speed and working memory, two skills known to be most commonly affected in MS patients and believed to be core deficits (DeLuca et al., 1998; Denney et al., 2004). We had several a priori hypotheses about the outcome of the study. First, it was hypothesized that information processing speed and working memory training would be associated with improved performance on separate neuropsychological tests that measure these skills. Our results showed significant improvements in scores on the PASAT, a test of information processing speed. The gains on this test were also significant for many participants in the study when we conducted a reliable change index analysis on individual scores. Second, it was hypothesized that information processing speed and working memory training would be associated with improved performance on neuropsychological tests that measure other, associated skills. Our results also showed significant improvements on the COWAT, a test of executive function. However, these results did not remain significant following the application of the Bonferroni correction, and as such should be considered a trend worth exploring in larger studies. Our data also supported some findings that trended toward statistical significance: scores on LNS (a working memory task), CPT (an attention task), and BVMT (a visual memory task).

Finally, it was hypothesized that participants who were more adherent to the training program would show greater improvements on cognitive outcome measures. We did not have sufficient variability in our adherence data in order to address this planned analysis.

We also conducted some secondary analyses. We found no effect of training on self-reported anxiety, depression, fatigue, or quality of life. We found similar effects on outcome measures when we analyzed only data from participants who adhered to more than 80% of the scheduled training. Additionally, the majority of our participants were satisfied with the overall study, training programs, and length of the training sessions and program.

This study aimed to utilize a specific cognitive training program to improve information processing speed and working memory in MS patients. Taken together, the results of our study suggest that targeted cognitive training was able to improve information processing speed, as evidenced by results from the PASAT, and trended toward improving working memory, as evidenced by results from the LNS. However, we did not find significant effects on all measures of processing speed or working memory, nor did we show improvements on all other, associated cognitive skills.

There are several things to consider as we draw implications about these findings. First, it should be noted that this project was a pilot study with a relatively small number of participants in each group (n = 20 per group). Our findings are encouraging given the small sample size, and it is possible that a larger study might produce findings that more strongly point to improvements in a particular cognitive area. A larger study might show improvements on more tasks of information processing speed and working memory, not just one. Second, many neuropsychological tests measure multiple skills. This makes interpreting the significance of score improvements somewhat challenging. For instance, achieving a high score on the PASAT requires not only information processing speed, but attention, concentration, and some working memory skills. Therefore, the improvement in scores seen in this study may be due to an improvement in just one or all of the aforementioned skills. Or, perhaps the improvements we observed on the PASAT are reflective of improvement in the ability to organize multiple skills to work together in consort.

There are several strengths of this study. Namely, we were able to make several important methodological improvements that we hope will contribute to the current literature. Notably, we were able to conduct a double-blind, randomized, controlled trial of cognitive training, wherein the control group was comprised of MS patients who engaged in sham training tasks that exactly resembled the active training tasks. Our participants were provided with computerized tasks that focused training on two key skills: information processing speed and working memory. Neuropsychological testing involved the use of counterbalanced measures (with alternate forms where available) that are validated and recommended for use with MS patients. Finally, we collected objective data on adherence to the training program.

It is important to compare our findings to those of other cognitive training studies in MS. Overall, these studies tended to find improvements that were limited to just one measure of a particular domain of functioning, much like the findings of this study. Taken together, results in this body of literature suggest that further inquiry is needed in order to better understand why training improves scores in such circumscribed areas and to bolster the efficacy of cognitive training for MS patients. Additionally, it is essential to note that these studies applied different cognitive training protocols in a different methodology. For instance, Brenk and colleagues (2008) applied non-specific training in their study and found improvements in visuoconstruction and visual delayed memory. Our study did not employ a measure of visuoconstruction, but we did find a trend toward significance on a measure of visual memory, the BVMT. Brenk and colleagues (2008) used a different measure of visual memory, so direct comparisons between measures cannot be made. Also, this study did not provide a description of the training tasks, so it is not possible to determine whether any aspect of the training was contributing to their findings.

Hildebrandt and colleagues (2007) applied a cognitive training program focused on memory and working memory and found improvements in immediate and delayed verbal memory, and working memory. Specifically, they employed a different measure of verbal memory than we used in our study, but we did not find any improvements in verbal memory from our training. One reason why our findings were discrepant could be that we did not attempt to target memory with our cognitive training, as our training focused solely on executive functions. They also found significant improvements on the PASAT (which they deemed a task of working memory), consistent with our study.

Shatil and colleagues (2010) found improvements in verbal and visual memory, but did not use tests validated for use with MS patients to measure these domains. Vogt and colleagues (2009) found improvements in working memory on digits backward and the PASAT, which are similar to our findings. They also found improvements on a measure of attention we did not use, and improvements on the MFIS, which we did not find in this study. Solari and colleagues (2004) only found improvements on verbal fluency, whereas in our study we had a trend finding on a verbal fluency task. Mattioli and colleagues (2010) also found improvements on the PASAT, alone with an improvement on a task of executive functioning we did not use in our study. Finally, several studies in this literature found improvements in domains we did not measure (Jønsson et al., 1993; Plohmann et al., 1998; Tesar et al., 2005). In sum, our findings are reasonably consistent with those of other studies in this literature, and lend further credence to the notion that cognitive skills can be improved in this population.

One limitation of this study is the exclusion of potential participants who do not own a home computer or have access to broadband internet services. This limitation therefore restricts our findings only to MS patients who own and use a home computer. However, we believe this exclusion was necessary, as we intended to study an intervention that could be implemented in the home. Another limitation of the study is that we did not include a measure of functional daily living skills, which would have allowed us to better determine the real-world implications of improvements on neuropsychological tests. Additionally, we included both cognitively impaired and non-impaired patients. We chose not to screen for cognitive impairment for several reasons: 1) patients may have experienced cognitive decline but would not be considered impaired according to neuropsychological testing; 2) all MS patients have the potential to make gains in cognitive training; 3) we wanted to determine the effect of focused cognitive training on the general population of MS patients; and 4) we believe there is a great potential to use cognitive training prophylactically to increase cognitive reserve and slow future cognitive decline, even before measurable impairments in cognitive functioning are present. Additionally, our pilot study sample size is small, and follow-up replication is recommended in order to confirm these findings.

Another limitation is the relatively large attrition rate. Thirty-one (or 44%) of the originally enrolled participants left the study prior to completing study requirements.

Attrition did not appear to be measurably larger from either group. The large attrition rate could be due to several factors, including the challenging nature of the tasks or the amount of time required of participants. It is important to note that this attrition rate appears to be similar to those in other studies of adherence to long-term interventions, both in MS and other chronic disease groups (Shatil et al., 2010; World Health Organization, 2003). More research is needed in order to identify reasons why MS patients either do or do not comply with this type of intervention. Future studies should consider utilizing regular phone check-ins that involve motivational interviewing counseling techniques to improve adherence rates. Finally, this study did not investigate differences in improvements between subgroups of MS patients (e.g., those with and without measurable impairments, or participants with different MS-subtypes). Research in larger samples would allow identification of patients who will benefit from cognitive training.

Some questions about the applicability of cognitive training in MS patients still remain, and these are important to note when considering future directions. Most importantly, as previously stated, follow-up studies with larger sample sizes are needed in order to determine whether the results of this pilot study survive such scrutiny. Based on our findings, it appears that focused training does indeed have a positive effect on aspects of attention and processing speed, with data trending toward effects on verbal fluency, working memory, and visual memory. However, we hypothesized that training very specific skills would result in improvements seen in neuropsychological tests that measure those skills, which was not entirely supported by our findings. A larger-scale study would better illuminate the effect of focused cognitive training in this population. Future studies should consider adding a second follow-up evaluation after a period of no training, as it is important to establish whether any gains during training remain once it is complete. Additionally, future research should consider incorporating fMRI correlates of improvements made during cognitive training. Finally, future studies might also consider including a measure of functional activities of daily living in order to better appreciate the effect of cognitive training on real-world outcomes.

In summary, our results suggest that computerized, home-based cognitive training focused on information processing speed and working memory in MS patients can successfully produce improvements on cognitive skill, as measured by neuropsychological tests. Specifically, we found improvements on attention and processing speed (as measured by the PASAT), and results that trended toward significant improvements on executive function (COWAT), working memory (LNS), visuospatial memory (BVMT), and attention (CPT). These findings are encouraging given the fact that our study was a small pilot project with a relatively small number of participants. We were able to successfully make methodological improvements, such as including a sham training control group of MS patients. Limitations of our study include the fact that we did not include a measure of functional daily living skills, participants were not screened for potential cognitive impairment for inclusion, and the project was a relatively small pilot study with a large attrition rate. Future studies should aim to implement this cognitive training program with a larger number of patients and consider adding a second follow-up evaluation that would occur after a period of no training, to determine if gains made during training persist. Finally, future studies should also consider including a measure of functional daily living skills, as well as examining the neuroimaging correlates of improvements made in cognitive training using structural and functional MRI.

ILLUSTRATIONS

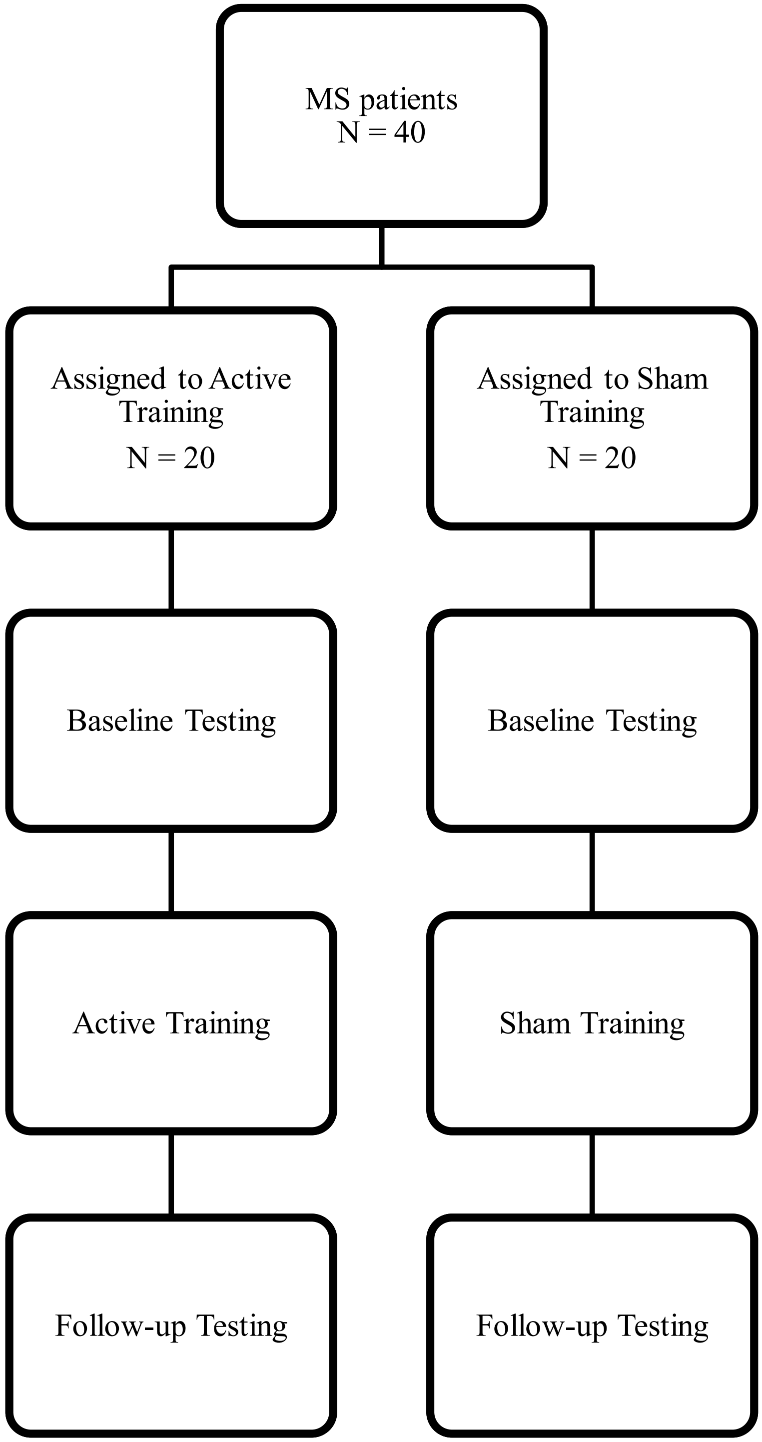


Figure 1. Flowchart depicting the general timeline of the study for participants in both conditions.

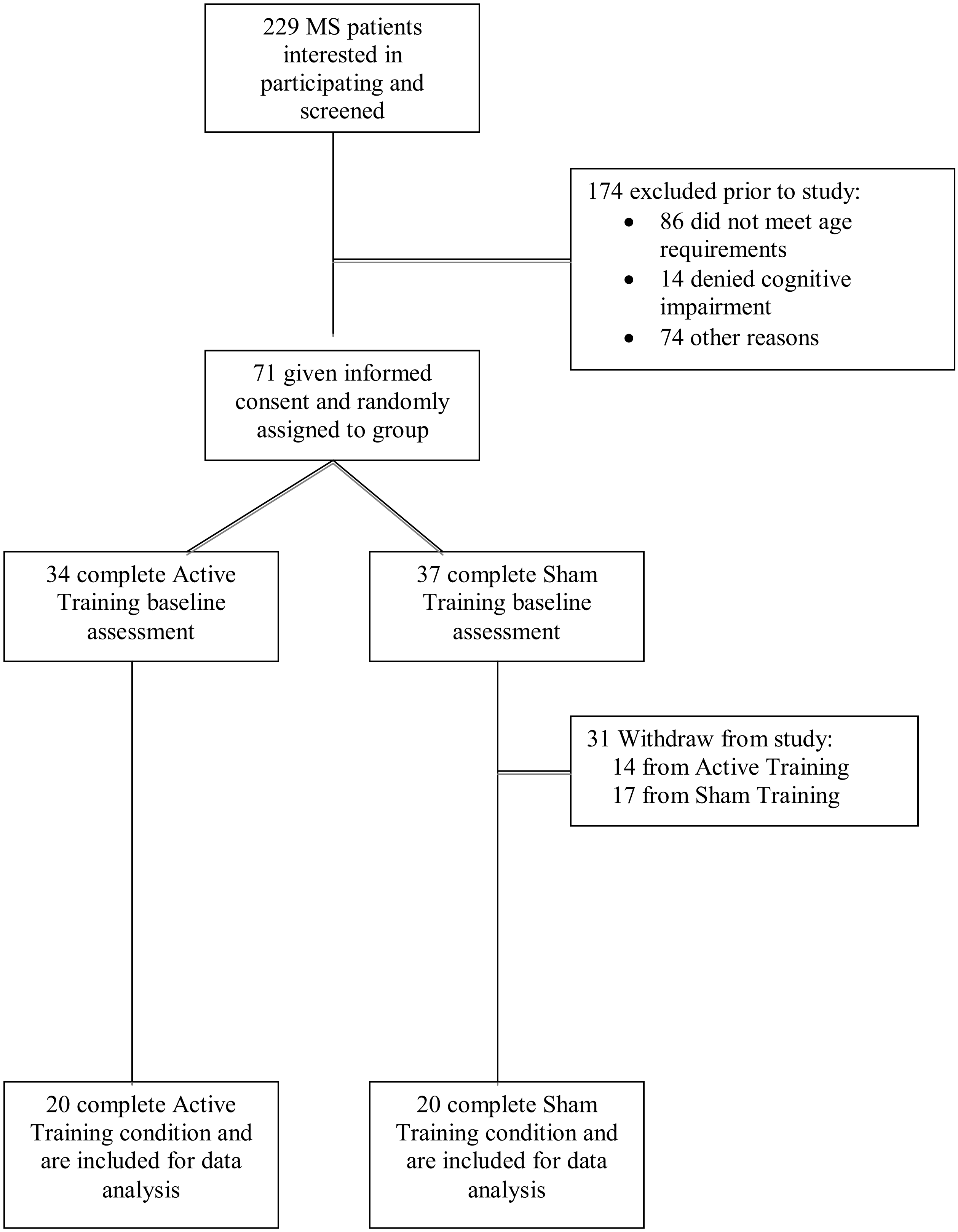


Figure 2. Flowchart depicting the recruitment process for the study.

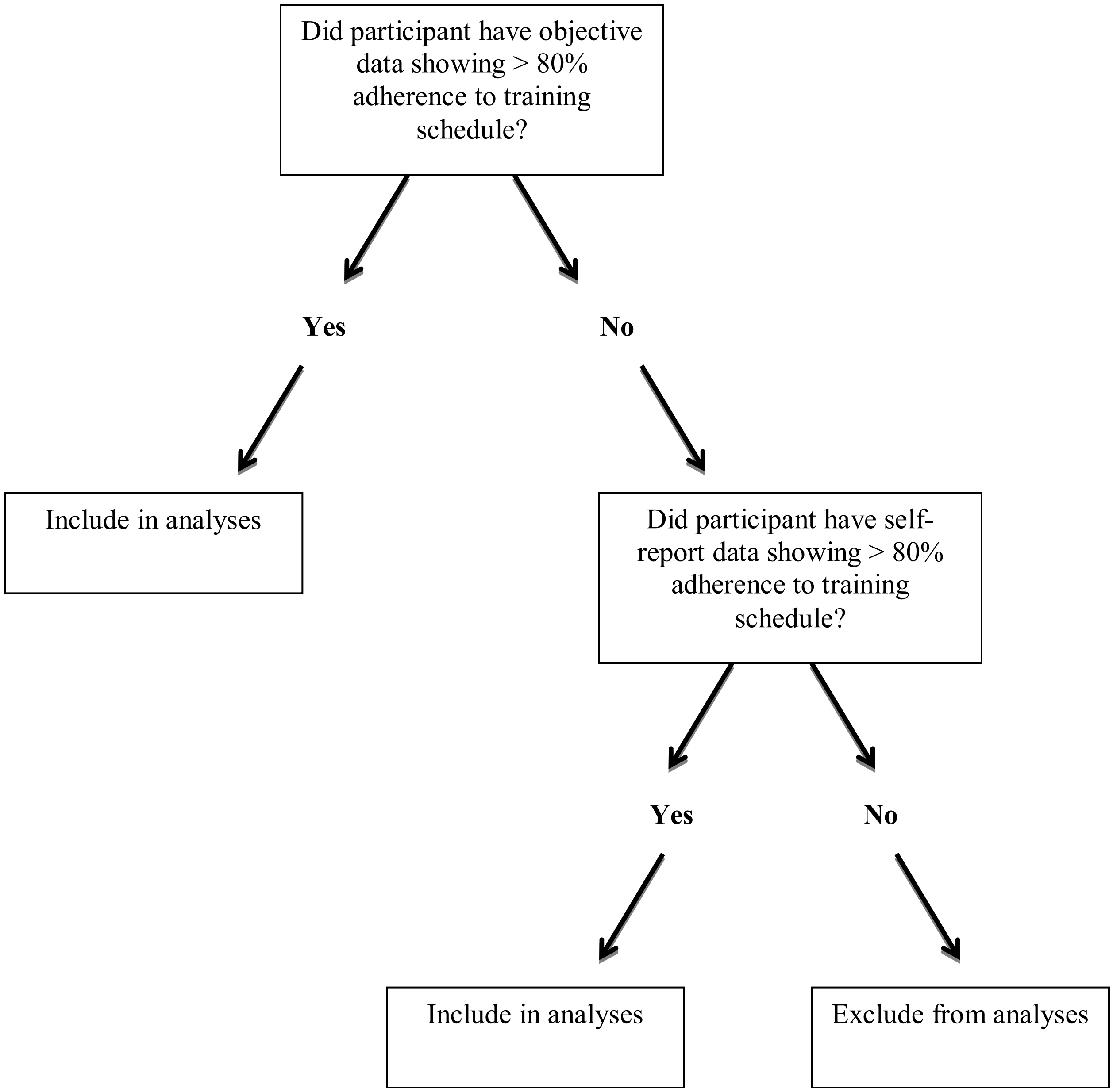


Figure 3. Decision-tree used for determining when to eliminate data from secondary analyses.

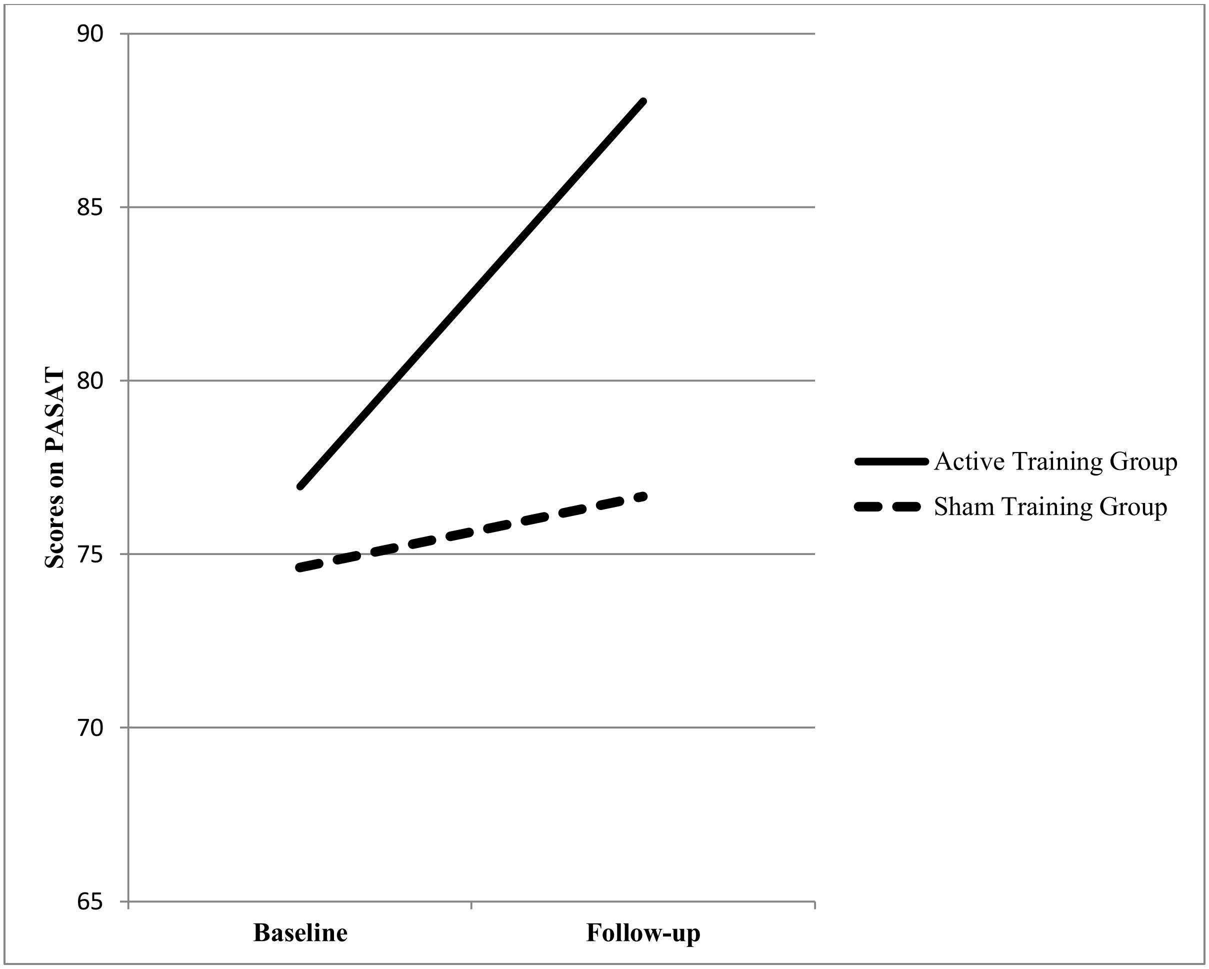
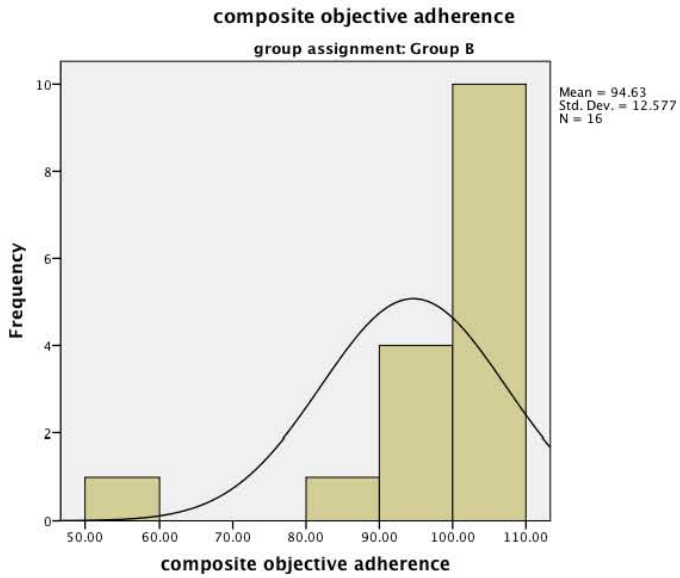


Figure 4. The interaction effect on scores on the PASAT is depicted here. A within-subjects analysis confirmed that there was significant improvement in the PASAT scores across time in the Active Training group. By contrast, no difference was found for the PASAT across time in the Sham Training group.



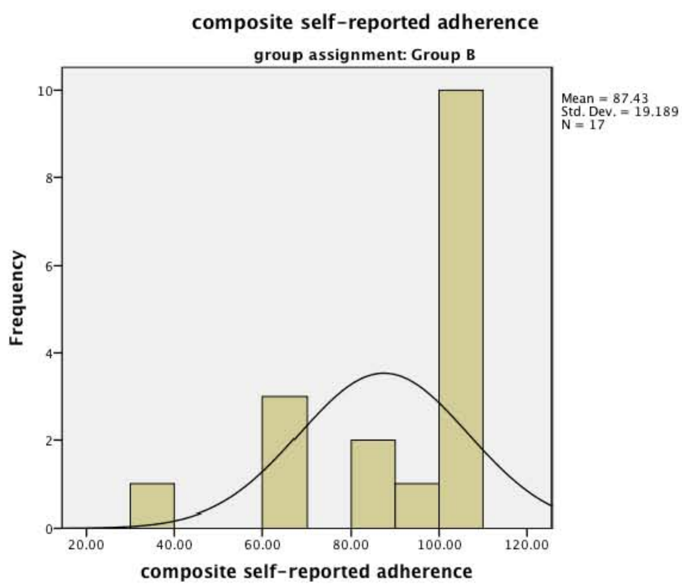


Figure 5. Histograms showing the distribution of adherence scores for each reporting method for participants in the Active Training group.

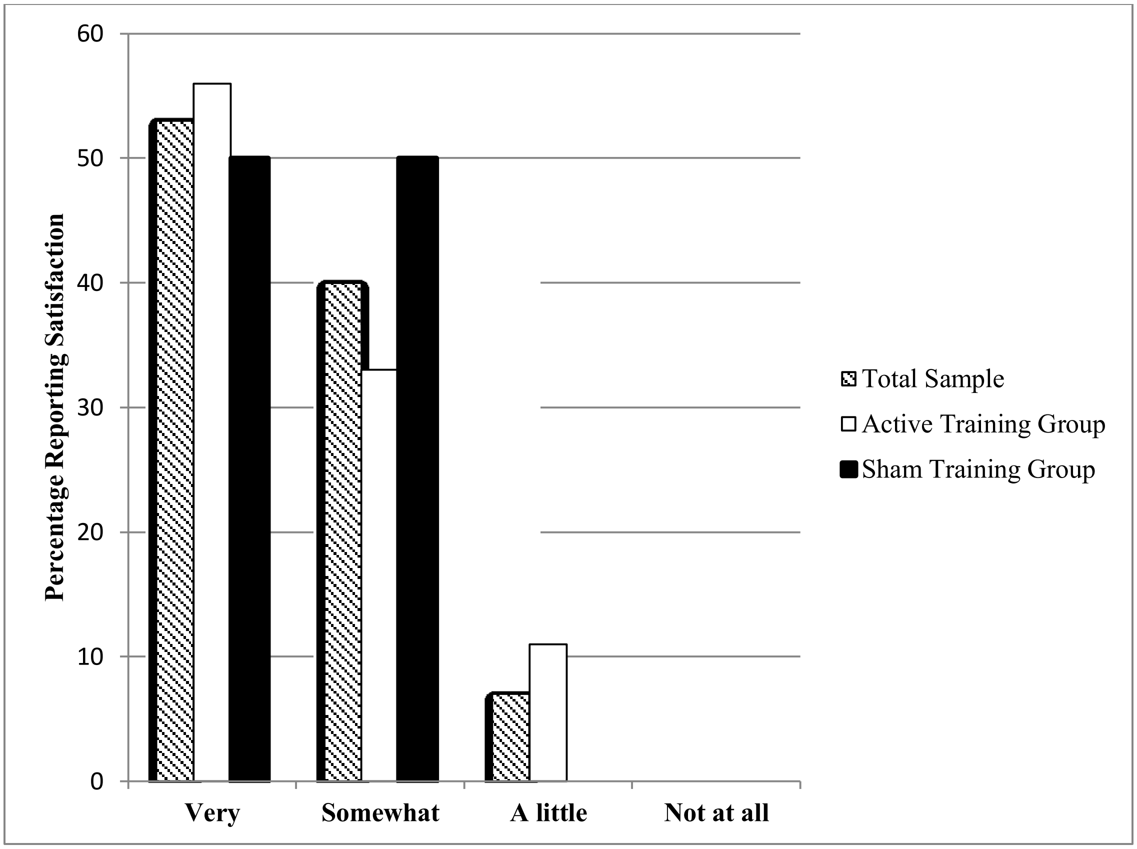


Figure 6. Illustration of the degree of participant satisfaction with the overall cognitive training program. Data are presented for both the total sample and participants in each group.

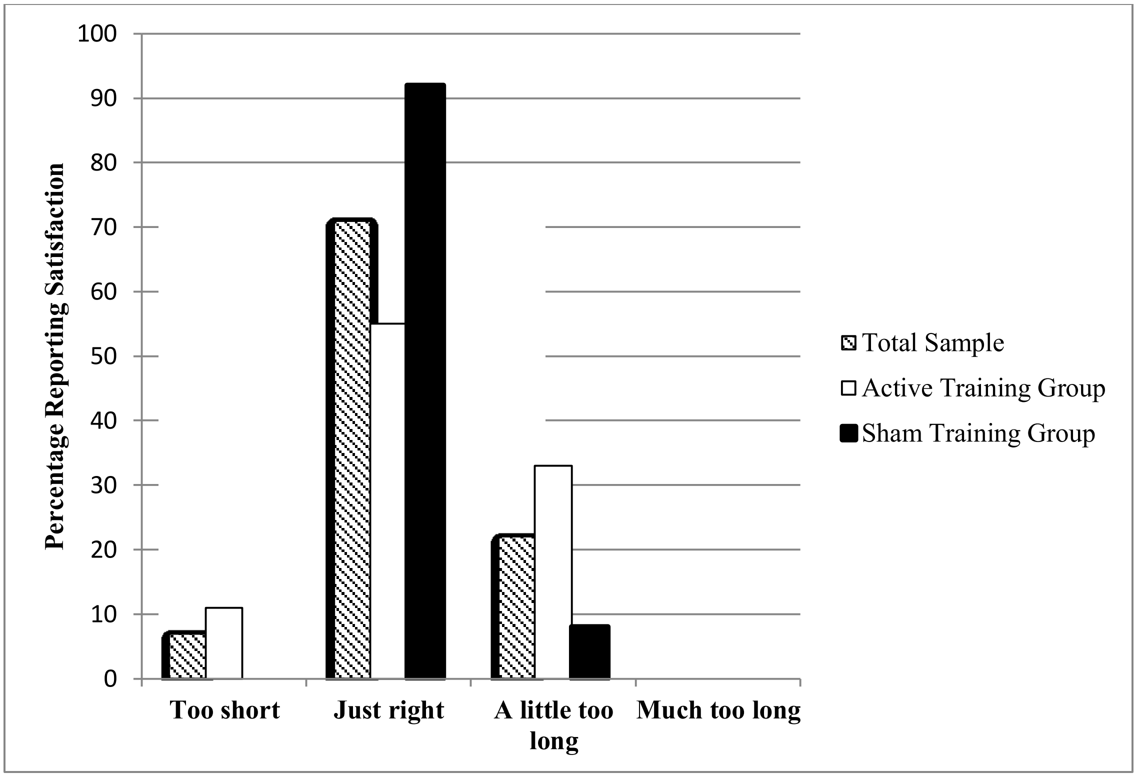


Figure 7. Illustration of the degree of participant satisfaction with the individual cognitive training sessions. Data are presented for both the total sample and participants in each group.

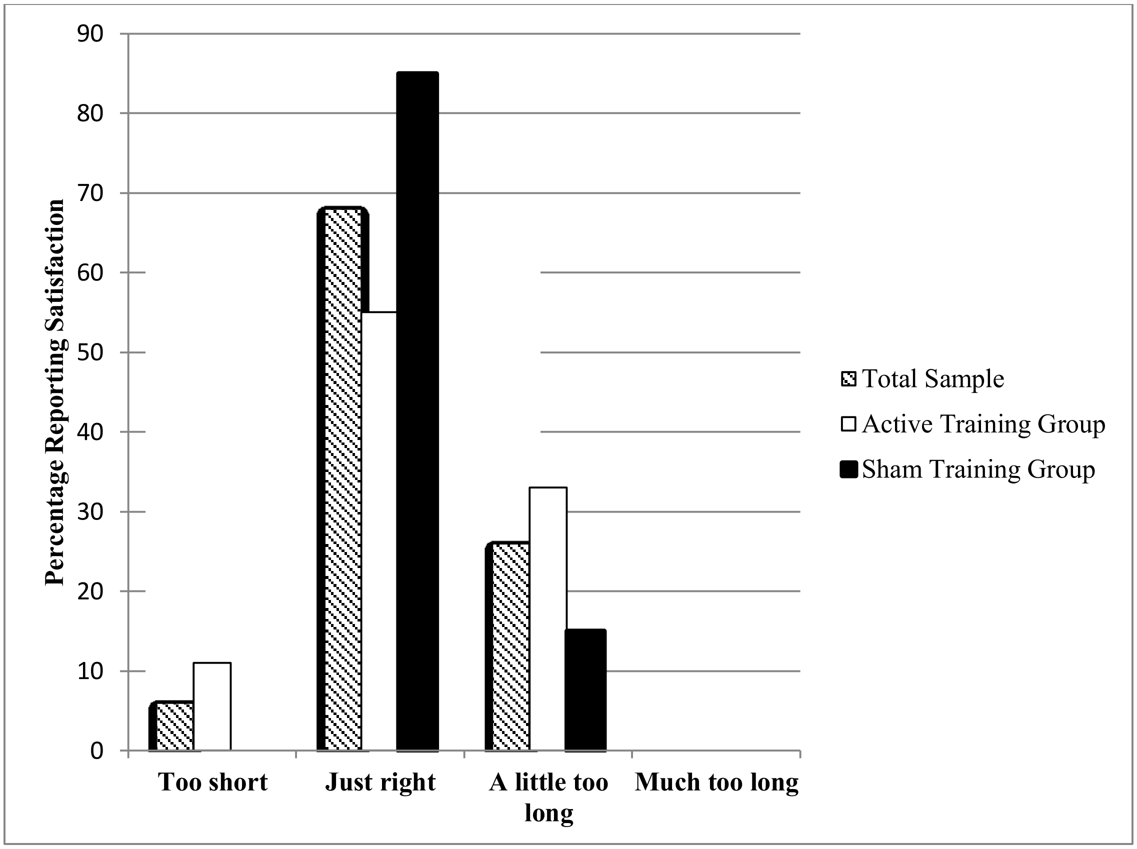


Figure 8. Illustration of the degree of participant satisfaction with the total cognitive training schedule. Data are presented for both the total sample and participants in each group.

APPENDIX A

List of Neuropsychological Measures Administered

Multiple Sclerosis Functional Composite (25-foot walk, 9-hole peg test, PASAT)

Visual Acuity Exam

Rey Auditory Verbal Learning Task

Brief Visuospatial Memory Test

Stroop

Conners' Performance Task-2nd Edition

Wechsler Test of Adult Reading

Controlled Oral Word Associations Task

Digits Backward

Computerized Assessment of Response Bias

Symbol Digit Modalities Test

Letter-Number Sequencing

APPENDIX B

List of Questionnaires Participants Completed

Sleep Questionnaire

Medication Adherence Questionnaire

Prospective and Retrospective Memory Questionnaire

Current Fatigue Impact Scale

Self-Report of Cognitive Impairment Scale

State-Trait Anxiety Inventory

Beck Depression Inventory-Fast Screen

Modified Fatigue Impact Scale

Processing Speed Questionnaire

NEO-Five Factor Inventory

Epworth Sleepiness Scale

Multiple Sclerosis Quality of Life Inventory

Computer Use Questionnaire

APPENDIX C

Jacobson-Truax Formula

$$\text{Reliable Change (RC)} = \frac{x_2 - x_1}{S_{diff}}$$

$$S_{diff} = \sqrt{(2S_E^2)}$$

Standard Error Measurement (S_E) = $SD\sqrt{(1-r_{xy})}$

The change score is calculated by subtracting each participant's post-test score from their pre-test score, and then dividing that value by the standard error of difference between the two test scores. The test-retest reliability of the PASAT was 0.951.

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VITA

Laura Mitchell Hancock was born in North Dakota but raised mostly in Wichita, Kansas. She was educated in local public schools and graduated from the International Baccalaureate Program at Wichita High School East, where she was also an Academic All-American Swimmer, in 1997. She received a Medallion Scholarship to Kansas State University in Manhattan, Kansas, from which she graduated in 2001. Her degree was a Bachelor's of Science in Psychology. Ms. Hancock then attended Washburn University in Topeka, Kansas, from which she graduated, Phi Kappa Phi, in 2004. Her degree was a Master's of Arts in Clinical Psychology.

After working as a Licensed Master's Level Psychologist for KVC Behavioral HealthCare, Inc., in Kansas City, Kansas, and a state psychiatric hospital in Osawatomie, Kansas, she began work toward her Ph.D. in Clinical Psychology at the University of Missouri-Kansas City in the Fall of 2008. Since 2008, Ms. Hancock has been working on research projects examining the neuropsychological impact of multiple sclerosis. She was awarded the UMKC School of Graduate Studies Arthur Mag Fellowship for 2010-2011 and the UMKC School of Graduate Studies Chancellor's Fellowship for 2011-2013. Upon completion of her degree requirements, Ms. Hancock will complete a postdoctoral fellowship in Clinical Neuropsychology at the Alpert Medical School of Brown University, where she will focus on pursuing both clinical and research interests.

Ms. Hancock is a member of the International Neuropsychology Society, the National Academy of Neuropsychology, and the American Psychological Association.