The Effects of Cognitive Training on Executive Functioning and Attention in Multiple Sclerosis

Thesis

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Abstract

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system that results in diffuse nerve damage and associated physical and cognitive impairments. Of the few comprehensive rehabilitation options that exist in the MS literature, those that have been successful at eliciting broad cognitive improvements have focused on a multi-modal training approach that emphasizes complex cognitive processing utilizing multiple domains simultaneously. The current study sought to determine the feasibility and effectiveness of an eight-week, hybrid variable priority (HVT) training program, using the video game, Space Fortress, relative to a wait-listed control group, to remediate cognitive deficits in a group of individuals diagnosed with relapsing-remitting MS. Twenty-six participants were recruited for the study and randomized to either a training group or a wait-listed control group. To assess broad transfer, a battery of neuropsychological tests was administered to all participants pre- and post-intervention. The results indicated an overall improvement in skill acquisition, as evidenced by a significant improvement in total game score, but a lack of transfer to any tasks of cognition functioning as assessed by the battery. Participants in the training group, however, did show improvements on the 9-hole Peg test, a measure of fine motor control. Improvements to the current model would include a longer training course to elicit positive performance values, the inclusion of only cognitively impaired individuals, and integration of subjective measures of improvement in addition to objective tests of cognitive performance.
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I would like to dedicate this manuscript to my parents; my first mentors, and my dearest friends.
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Chapter 1
Introduction

Multiple Sclerosis (MS) is one of the most frequently diagnosed neurodegenerative diseases among adults in the U.S. with a current prevalence of approximately 400,000 cases (nationalmssociety.org, Poser et al., 2007). In contrast to other common neurological disorders, this disease typically affects individuals in the prime of their adult life with an average onset between 20-50 years of age, with women receiving a diagnosis two to three times as often as men (nationalmssociety.org). MS is more prevalent in individuals with European ancestry as compared to individuals with Asian, African American or Hispanic decent (nationalmssociety.org). According to recent estimates, the worldwide prevalence of MS is around 2.5 million people with an estimated annual cost for one individual exceeding $57,000 annually, and lifetime expenses exceeding $2.2 million. Lost wages account for almost one third of each individual’s annual financial burden, exceeding costs associated with health care or medications (Whetten-Goldstein et al., 1998). Antecedents to job loss and subsequent lost wages include the many physical and cognitive declines associated the MS disease course.

MS involves progressive and unpredictable episodes of axonal demylenation and transection (Compston & Coles, 2002). This nerve damage results in lesions along axons
of the brain, brain stem, spinal cord and optic nerves (Compston & Coles, 2002). The leading etiological theory attributes these neurological assaults to an autoimmune attack on the oligodendroytes that maintain and synthesize the myelin of the central nervous system (CNS) (Compston & Coles, 2002). Loss of axonal integrity due to myelin destruction in the CNS results in delayed conduction of evoked potentials, spontaneous axonal discharge, and increased mechanical sensitivity (Compston & Coles, 2002). This interference with normal axonal communication has been associated with motor, sensory, psychological, visual, bladder, sexual, and cognitive symptoms commonly experienced by individuals with MS (Calabrese, 2006 review, Devins et al., 1987).

These symptoms follow a variable pattern over the course of the disease and across differential subtypes of MS. Diagnostic criteria require the dissemination of focal lesions within the CNS across time and space, usually identified via magnetic resonance imaging (MRI) (Polman et al., 2011). The disease pattern is known to follow a variable path and can be characterized by either acute episodic periods of worsening (exacerbations), gradual progressive deterioration of neurologic function, or a combination of these two (Lublin & Reingold, 1996). The results of an international survey by Lublin and Reingold defined 5 different types of clinically-definite MS diagnoses associated with distinctive combinations of these unpredictable patterns (1996). These include relapsing remitting, primary progressive, secondary progressive, relapsing progressive, and progressive relapsing, the most prevalent of these being relapsing remitting MS (RRMS). The defining characteristics of RRMS are “episodes of acute worsening of neurologic function followed by a variable degree of recovery, with a stable course in between attacks” (Lublin & Reingold, 1996). These attacks are generally
defined by their outward physical symptoms, including temporary paralysis and numbness of the extremities, with function returning partially or in full after the exacerbation. Cognitive declines associated with the disease course are less overtly discernable in comparison to physical or affective symptomatology, are not typically associated with neurological disturbances that constitute an “attack”, and can appear independently of physical symptoms, complicating their identification and recognition (McDonald et al., 2001; Cobble, 1992). For the purpose of this study, considering the greater prevalence of RRMS patients in comparison with other diagnoses, we will focus our intervention on this group of individuals. Similarly, all further literature referenced within this review will be associated with RRMS individuals exclusively.

Cognitive Impairment

Recent estimates suggest that 43-70% of individuals with MS suffer from cognitive deficits, with initial impairment frequently occurring early in the disease course (Pelosi et al., 1997; Piras et al., 2003). Evidence of these early cognitive deficits is apparent in individuals with clinically-isolated syndrome (CIS), a precursor to the clinically definite MS diagnosis. A recent cross-sectional study of 40 CIS patients examined the extent of cognitive decline in multiple domains including attention, concentration, speed of information processing and abstract reasoning (Feuillet et al., 2007). Compared to a group of age, gender and education matched healthy controls, 57% of CIS patients demonstrated cognitive impairment across all tested domains, further supporting the appearance of significant cognitive deficits early in the disease course. This amount and prevalence of cognitive decline preceding clinically definite diagnosis
lends support to the use of cognitive rehabilitation throughout the disease course, regardless of disease duration.

Individuals with clinically-definite MS also exhibit significant impairments in cognition, however, the progression of these impairments is moderated by disease subtype. Several cross-sectional studies have supported significant differences in cognitive impairment across MS subtypes, with progressive diagnoses exhibiting greater general cognitive impairment in addition to pronounced specific impairment in the area of information processing (Denney et al., 2005; Huijbregts et al., 2004 & 2006). These differences also exist longitudinally, with progressive subtypes exhibiting greater decline in information processing abilities across time as compared to relapsing-remitting individuals (Bergendal et al., 2007). Comparatively, RRMS individuals display lesser degrees of cognitive impairment, but also represent the most prevalent disease subtype and, thus, the largest proportion of cognitively impaired individuals. A meta-analytic investigation within our own lab provided evidence for the presence of significant cognitive impairments in individuals with RRMS, relative to healthy controls (Prakash et al., 2008). Overall, this study revealed a moderate effect size of 0.539 for a general cognitive impairment in RRMS individuals as compared to healthy controls, with largest detriments observed for domains of motor functioning (g=0.728) and memory and learning (g=0.607). In addition, the results of the meta-analysis also provided evidence for impairments in the areas of attention and executive functioning (g=0.555), which was further divided to include information processing speed (g=0.646), working memory (g=0.515), short term storage capacity (0.430), sustained attention (0.565), and
The two sub-domains of processing speed and working memory, together, constitute the concept of information processing efficiency, or the ability to manipulate information in the brain for a short period of time (working memory) and the speed with which one can manipulate or process that information (processing speed) (Salthouse & Mitchell, 1989; Baddeley, 1992; Archibald and Fisk, 2000). Deficits of information processing efficiency in RRMS patients have been illustrated across a number of working memory paradigms including several forms relying on both verbal abilities as well as mathematical fluency (Lengenfelder et al., 2006; Parmenter et al., 2007; Archibald and Fisk, 2000). However, multiple studies have suggested that the main source of information processing efficiency deficits stems from a general slowing of mental processing speed. In a study of 215 RRMS patients, impaired information processing efficiency was tested within multiple cognitive domains, revealing a main deficit of processing speed as the driving effect in information processing declines (DeLuca et al, 2004). In further support of this theory, a recent study was conducted that examined working memory accuracy at differing levels of processing speed and cognitive load (Leavitt et al., 2011). The investigators found that when MS individuals are given additional processing time to encode information that is comparable to the cognitive load of the task, performance decrements on working memory paradigms significantly improve. Information processing efficiency impairments are reduced when individuals are given enough time to fully encode the information in short-term memory, further exemplifying the interdependence of these two sub-domains. A successful cognitive
intervention must focus not only on ameliorating processing speed deficits, but also the complex integration of processing speed with mental manipulation to improve information processing efficiency.

The robust impact of processing speed deficits on multiple cognitive domains including information processing efficiency is predictive of long-term impairment, with a pronounced decline in processing speed occurring over several years of follow-up (Bergendal et al., 2007). In addition, this longitudinal decay in processing speed performance is significantly correlated with disease progression as measured by the Expanded Disability Status Scale (EDSS), a metric scale of neurological disability widely used in the MS population (Bergendal et al., 2007, Kurtzke, 1983). These impairments do not appear to be modality specific (auditory vs. visual perception), and are largely reduced when the patient is given adequate time to process information (Demaree et al., 1999). Along these lines, it is reasonable to assume that an increase in processing speed would be effective across modalities and result in improvements in associated cognitive domains. In order to ameliorate declines in additional cognitive domains that are confounded by processing speed impairments, such as executive functioning, and information processing efficiency, initial gains in processing speed would be essential to a comprehensive cognitive rehabilitation program. Through the use of a complex video game paradigm, we hope to focus on retraining working memory and processing speed sub-domains initially in isolation to improve performance, as well as integrating them into a complex situational learning environment to merge information processing efficiency improvement with larger executive functioning gains.
Executive functioning consists of higher order cognitive functions including planning, abstract and conceptual reasoning, fluency, and organization. Deficits in these domains can affect up to 17% of MS patients (Drew et al., 2008). Research with healthy control populations has revealed three distinct factors that comprise the executive functioning domain including mental set shifting, information updating and monitoring (similar to working memory), and inhibition of dominant or automatic responses (Miyake et al., 2000). These factors appear statistically distinguishable, but also show some commonality in their dependence on the single unitary construct of executive functioning (Miyake et al., 2000). All of the sub-domains listed in our previous meta-analysis are related with at least one of these factors including information processing efficiency (information updating), sustained/selective attention (inhibition and mental set shifting), and short term memory capacity (mental set shifting and working memory) (Prakash et al., 2008; Miyake et al., 2000). Possibly as a product of this unitary, underlying construct observed in younger adults, RRMS individuals exhibit deficits in all three executive functioning domains. In a task of mental shifting, as measured by the task-switching paradigm, a group of 22 RRMS patients showed significant impairment in endogenous set-shifting, or advance preparation for the target shifted task, than an equal group of healthy controls (Stabulum et al., 2004). In an illustration of deficient inhibitory processing, 58 RRMS patients were tested on the Stroop task, which requires patients to respond to the color of ink a word is written in rather than the word itself (Deloire et al., 2005). MS patients exhibited significantly poorer performance than age and gender matched healthy controls when the stimulus was incongruent, i.e. the word blue written in yellow ink. They were less able to inhibit the natural response to read the color word as
opposed to responding to the ink color, signifying a lack of attentional inhibition. As previously noted, deficits in information updating and monitoring are highly affected by information processing efficiency deficits resulting in impaired working memory performance (Janculjak et al., 2002, Leavitt et al., 2011; DeLuca et al., 2004). Taking into account the commonality of deficits across all three of these executive functioning factors, it is clear that an effective intervention would target domain specific retraining focused on each factor of executive functioning, as well a convergence of these factors in complex goal-directed tasks based on their unity under the executive functioning domain.

In our rehabilitation program, with a focus on each individual portion of the more complex game, each of these executive functioning sub-domains will be targeted separately. Subsequently, in the combined full game, we will focus on the common factor underlying these executive functioning deficits by combining all three factors in complex, goal-directed video game play.

As the findings of our meta-analysis and the previous factor analysis illustrate, selective and sustained attentional processes can also be subsumed under the umbrella of executive functioning (Miyake et al. 2000; Prakash et al., 2008). These two domains are frequently combined within the MS literature due to their dependency on one another for successful cognitive performance (Prakash et al., 2008). In support of this fact, previous research has shown that MS patients show similar accuracy performance to healthy controls on tasks of automatic attentional processing (Paul et al., 1998). Impairments were only introduced when effortful attention was involved in tasks of executive functioning such as working memory paradigms (Paul et al., 1998). Similarly, multiple recent studies of attentional impairment have exhibited declines within effortful domains,
such as divided attention, in the form of multi-task paradigms as well as inhibitory processing (Nebel et al. 2007; Kavcic & Scheid, 2011). While many of these studies define their investigations as focused on attention, the paradigms employed rarely are purely attentional and almost always require executive functioning demands. One such study that did include automatic attentional processing in the form of simple focused attention did not demonstrate significant impairment in RRMS individuals (Dujardin et al., 1998). Additionally, most intervention paradigms that target attentional retraining are focused on executive functioning factors such as inhibition or working memory (See Penner & Kappos, 2006 for review). Based on this review, simple attentional processes appear to be unaffected in MS, while reports of decline in executive attentional control are widespread. Those studies that do report attentional impairment have a broad focus on attentional control that also involves a multitude of higher order functions. This is possibly associated with the same shared variance that affects all executive functioning factors (Miyake et al., 2000). Equivalently, it is imperative that any successful cognitive intervention should target a more comprehensive rehabilitation paradigm that incorporates attentional retraining as a function of goal-directed executive behavior.

The deterioration of these cognitive abilities across time is also associated with significant declines in multiple quality of life domains. Past research has established a strong association between scores on quality of life outcome measures and cognitive impairment status in this population. In a seminal study, Rao and colleagues found that individuals with MS who were cognitively impaired participated in fewer social and vocational activities, were less likely to be employed and were more vulnerable to psychiatric illness than patients with purely physical disabilities (Rao et al., 1991). More
recently, these findings were revisited in an investigation that illustrated the strong predictive power of cognitive impairment on vocational status even after age, education, sex and depressive confounds were removed (Benedict et al., 2006). Specifically, in a sample of 291 MS subjects, those tasks that emphasized declines in verbal memory and executive functioning were the strongest indicators of vocational status, with poorer performers less likely to be employed. Further investigations have linked this threatened or actual loss of unemployment with a lower perceived quality of life and increased stress on the individual and their family unit (de Judicibus & McCabe, 2007). This strong association between cognitive functioning and social, occupational and psychiatric well-being provides a valid platform for intervention. If this progression of impairment can be interrupted or alleviated through cognitive rehabilitation, it is plausible that these associated quality of life factors would also improve, including occupational and psychiatric status.

**Cognitive Rehabilitation**

Currently, very few options exist to ameliorate cognitive declines in MS. Given that MS impacts individuals in the prime of their lives, and the financial expense associated with lost employment wages, cognitive rehabilitation could be a one possible solution to allow these individuals to continue contributing to society and lower their individual economic burden. While there are well studied and disseminated treatments for the physical impairments associated with MS, little exists for the treatment of cognitive impairments. The majority of the current research within the MS literature has focused on communication skills and memory rehabilitation with a limited concentration on attention
and executive functioning (See O’Brien et al., 2008 for review). Few comprehensive rehabilitation programs, such as the current proposed study, exist or have been empirically tested.

Those interventions that have been performed within the learning and memory domains have proven successful. Utilizing an elaborative encoding strategy to aid with initial information processing, Chiaravalloti and colleagues were able to demonstrate a 2 standard deviation improvement in 88% of their MS sample (Chiaravalloti et al., 2005). The elaborative encoding techniques administered by research assistants required patients to use both imagery and contextual clues during the encoding of information that would later be tested at recall. Additional learning and memory retraining paradigms have focused on computer-assisted programs as opposed to an individual, in person administration method. In a study by Mendozzi and colleagues, the effect of retraining memory impairments specific to each individual utilizing a computer-assisted program was contrasted with a comprehensive training approach focused on general memory impairments (Mendozzi et al. 1998). Results revealed that those patients that underwent a specific retraining program improved on 4 of 11 post-assessment memory tasks, supporting the efficacy of a computer-assisted training program as opposed to the more time intensive, personally administered strategy employed by Chiaravalloti. While both have been proven effective, a computer-assisted program is likely to be more financially feasible and less labor intensive for MS clinicians, possibly resulting in wider dissemination. Similarly, the proposed intervention paradigm has been designed as a computerized video game that could be widely disseminated across the internet as well as in rehabilitation centers.
Similar to Mendozzi et al., additional research paradigms have also explored the efficacy of an individualized training paradigm specific to each patient’s impairments as compared to a more comprehensive design. However, research in targeted cognitive domains other than memory exhibit mixed results. Solari et al. conducted a paradigm focused on retraining attention and memory deficits (Solari et al., 2004). Those individuals that received cognitive retraining specific to their individual deficits improved significantly on only one task of the BRB as compared to controls trained on general attention and memory impairments. However, limited power from diminished recruitment numbers could have reduced the ability to detect significant outcomes. Additionally, this study also employed multiple tasks that were focused toward specific aspects of attention and memory, rather than a broader approach that combines multiple cognitive domains into one comprehensive training program. A similar design by Plohman and colleagues focused on retraining specific attentional impairments in a group of 22 MS participants (Plohman et al., 1998). These individuals were screened for specific deficits in four domains of executive attentional control: divided attention, selective attention, vigilance, and sustained attention. Half of these individuals received a computer-assisted retraining program individualized to their specific executive attentional deficit for 12 sessions while the other half received a multi-focal training program that targeted all four attentional domains independently. After 12 weeks, the specific training group improved on two categories of executive control as well on subjective quality of life ratings. While a significant group x time interaction in favor of the specifically trained group did exist on 3 attentional tasks, these results were limited to reaction time data with no evidence of significant group differences on accuracy. The data also
supports significant improvements within the comprehensive group on all tasks as a function of the intervention. However, both of these studies focused on a practice based training approach of each cognitive domain independently. While this is likely to produce improved performance on the trained task, broad transfer is less likely. Even specifically designed cognitive testing paradigms are unlikely to target just one specific cognitive domain as it was trained. Broad transfer is dependent on multiple cognitive domains acting in concert to complete a complex task.

In support of this fact, a recent study by Vogt and colleagues focused on retraining working memory in MS participants (Vogt et al., 2009). However, rather than targeting specific functions of working memory through previously defined, domain specific tasks, these researchers chose to use a more comprehensive computer-based approach utilizing the software Brainstim. This program involves multi-modal cognitive processing aimed at retraining not only each aspect of working memory, but also how these separate sub-domains perform concurrently in a complex task environment. This multi-focal diffuse approach improved working memory performance on a number of paradigms as well as mental processing speed, an associated domain imperative for successful working memory function.

The use of comprehensive training to ameliorate cognitive deficits is further supported by training programs that target attentional remediation in addition to executive functioning and memory gains. Flavia and colleagues examined the efficacy of a comprehensive computer-assisted cognitive rehabilitation program relative to a no-contact control group (Flavia et al., 2010). The specific training procedure used included
computer simulated driving experiences as well as organizational planning exercises that required the simultaneous functioning of multiple cognitive domains. Results indicated cognitive improvements on tasks of information processing, executive functioning and attention including specific gains on the Paced Auditory Serial Addition Task (PASAT) (2 and 3 second delay condition) as well as the Wisconsin Card Sorting Task (WCST), a measure of mental set shifting. Similar studies have also substantiated the use of a comprehensive computerized training paradigm to induce broad cognitive improvements. In a study of 15 MS individuals, significant improvement on a neuropsychological composite score was observed after 5 weeks of a comprehensive computerized training program focused on integrative cognition (Sastre-Garriga et al., 2010). Although the training was not targeted at one particular cognitive domain, improvement was seen on tasks that require multiple cognitive faculties for successful performance such as the PASAT. In comparison to previous findings that have demonstrated training transfer to one or two specific domains as a result of practice, these studies support a comprehensive training paradigm inclusive to multiple cognitive domains with a focus on complex skill acquisition requiring integration of cognitive functioning across domains.

While the cognitive rehabilitation research is still in its infancy within the MS population, this has been a vibrant area of research within younger adults, with some studies providing evidence against the success of such programs in enhancing cognitive faculties in younger adults (Owens et al., 2010, Olson & Jiang, 2004), and some studies providing support for the use of such programs for this population (Jaeggi et al., 2008; Holmes et al., 2009). In a recent study, Owens and colleagues had 11,430 people practice a multitude of cognitive domains utilizing a computerized program administered over the
internet (Owens et al., 2010). Although improvements were observed on every practiced task, no effect of transfer was observed. However, limitations of this study include a lack of participant monitoring due to Internet administration (some subjects only practiced 10 min./day, 3 times/week) and a focused approach based on training specific domain functions. Rather than integrating all targeted cognitive domains into one multi-focal training approach, researchers chose to train each dimension separately utilizing tasks localized to one or two functions of each domain. Similar studies that have attempted this domain specific approach exhibit limited transfer effects as well (Dahlin et al., 2008; Olson & Jiang, 2004).

In contrast, several multi-focal training-based programs have produced broad transfer in young adult populations. In a study by Jaeggi and colleagues, a group of 70 healthy younger adults were trained on a demanding multi-component working memory task over the course of 19 days (Jaeggi et al., 2008). Results exhibit transfer effects to multiple domains of working memory as well as improvement on tasks of fluid intelligence. This multi-modal approach to cognitive training focuses on minimizing automation, limiting domain-specific strategies, and demands high cognitive workloads or high intensity cognitive engagement (Morrison & Chein, 2011). Similar approaches with a focus on multi-modal training have been substantiated across multiple studies with younger adults (Chein & Morrison, 2010; Holmes et al., 2009, Klingberg et al., 2005), children, (Jaeggi et al., 2011; Wass et al., 2011) and with older adults (Brehmer et al., 2011; Zelinski et al., 2011; Li et al., 2008). Where approaches based on retraining a single domain in isolation fail to take into account the interdependence of even simple
cognitive processes, comprehensive, multi-modal training focuses on retraining cognitive domains in their integration with one another.

A current theory behind this approach is increased probabilistic inference as a function of training (Green et al., 2010). This theory espouses that training on complex and demanding tasks, such as video games, strengthens the connection between sensory perceptions and integration of sensory information leading to more efficient use of evidence for complex problem solving across multiple modalities (auditory and visual). This strengthened relationship results in a more proficient use of evidence for decision making and increased probabilistic inference reaction times. Research suggests that a complex and demanding training approach, such as video games, induces processing speed gains and associated improvements in probabilistic inference, or the ability to estimate whether a choice is correct or not. In contrast, simply retraining sensory processing speed in the absence of a complex task would also likely increase information processing speed on modality and domain specific tasks. However, there is little evidence that these improvements would survive when they are combined with multiple other domains as is commonly necessary to perform everyday tasks (Owen et al., 2010; Dahlin et al., 2008; Olson & Jiang, 2004). The key to retraining cognition with effective transfer appears to lie in retraining the interaction and integration of cognitive processes, not in the specific improvement of each process independently through practice. Green and colleagues have found support for this theory specifically with their research on video game learning and transfer, which involves efficient information processing in the presence of a multitude of other cognitive demands (Green et al., 2010).
Furthermore, the use of a comprehensive video game retraining program has been substantiated within the healthy older adult population; a group that exhibits similar broad cognitive declines to MS individuals (See Verhaeghen & Cerella, 2002 for review). Basak and colleagues demonstrated the efficacy of a video game, “Rise of Nations” in eliciting cognitive transfer effects to tasks of executive functioning (Basak et al., 2008). After 23.5 hours of training, older adults showed improved performance on multiple tasks of executive functioning, with combined attentional and processing speed demands, as compared to a control group. Although the specific declines identified in aging are somewhat different from those observed in MS, this study supports the use of a computer-based cognitive rehabilitation program to ameliorate broad cognitive impairments. Specifically, this study lends credence to a computerized video game core-training paradigm designed for cognitive rehabilitation of multiple domains. This evidence of skill transfer within another clinical population, distinct from MS, reinforces the efficacy of the proposed comprehensive video game paradigm in ameliorating cognitive declines.

Taken together, the results of a number of cognitive retraining studies within the MS population suggest the necessity of a comprehensive training program that focuses on a multitude of cognitive constructs, and results in broad transfers. In this proposal, we aim to investigate the efficacy of a video game based training program that emulates a complex situational learning environment to improve deficits in multiple cognitive domains in individuals with RRMS. The proposed training program with its emphasis on executive updating and monitoring, set shifting, and attentional vigilance and inhibition could provide an ideal platform to enhance cognitive faculties in this population.
Additionally, in the proposed study, will employ a training strategy focused on Part-Variable Priority (PVP) that has been shown to be superior to practice alone (Lee et al., in review). This training strategy is in contrast to much of the previous cognitive rehabilitation research in the MS cohort, which primarily focuses on practice of cognitive tasks. The PVP approach will allow for faster rates of skill acquisition as well as greater retention of these learned skills over time (Lee et al., in review). More details on the PVP training strategy are provided in the next section.

*Space Fortress*

Space Fortress is a complex and demanding game that requires players to manage overlapping component tasks that target multiple cognitive domains including working memory, executive functioning, processing speed, attention and fine motor control. A full game description follows in the methods section of this proposal. Space Fortress was initially developed by cognitive psychologists to study complex skill acquisition in healthy younger adults (Donchin, Fabiani & Sanders, 1989). Since its initial development, Space Fortress has been utilized in several studies of learning and complex skill acquisition to investigate learning approaches within a video game format. In a recent study, Boot and colleagues contrasted two approaches to skill acquisition, transposed onto the Space Fortress format; full emphasis training (FET) and variable priority training (VPT) (Boot et al., 2010). Full emphasis training involved practicing the full game in its entirety, while variable priority training required players to emphasize different components of the full game, reducing the complexity of the learning process and promoting a more rapid rate of skill acquisition. This resulted in a higher rate and
overall level of game performance in the variable priority group, supporting the use of a learning approach that reduces skill complexity in a step-wise fashion. Individuals are more likely to accumulate skill knowledge and attain higher levels of performance if learning occurs incrementally rather than in mass.

Additional step-wise approaches have also been validated to increase the level and rate of skill acquisition. In a design by Lee and colleagues, a hybrid-variable priority training (HVT) strategy method was introduced. This learning program utilized the previously mentioned VPT method with an additional part-task learning paradigm. In part-task learning, the game was broken down into multiple smaller tasks that require less cognitive load. This allowed the player to learn each aspect of the game separately, and then combine these skills in later VPT training. Lee also examined whether these training methods exhibited transfer to a wide variety of cognitive tasks. The results indicated a significantly higher learning rate in those individuals trained with the HVT method as compared to FET, which was evident after only 10 hours of training. Transfer to other cognitive domains, however, was limited to those tasks that were especially similar to the Space Fortress design (Lee et al., in review).

The lack of transfer in the Lee et al. study employing a comprehensive training program could be attributed to a number of variables. Firstly, the study was implemented on a population of healthy younger college students who would be considered at the peak of their cognitive potential. It is possible that lack of training transfer was associated with cognitive ceiling effects; healthy college age adults at their cognitive peak show little benefit from a design aimed at increasing cognitive functioning. Comparatively, a study
by Gopher and colleagues that utilized Space Fortress to train Israeli air force pilots exhibited task transfer across a number of cognitive domains including actual flight simulation (Gopher et al., 1994). An earlier comparison of data obtained from Israeli and U.S. game players illustrates a significant differential in Space Fortress performance using the FET method (Donchin et al., 1995). Specifically, Israeli participants appeared to perform at a lower level than U.S. participants throughout the training period. A factor analysis conducted within these two groups on the cognitive performance profiles of each population subset revealed a significant deficit in processing speed in the Israeli participants as compared to their U.S. counterparts (Foss et al., 1989). While the origin or causal factor behind lower processing speed scores in the Israeli sample can only be speculated upon, it is possible that transfer effects are more likely in a population with lower cognitive abilities, like the Israeli sample, at the beginning of training. These individuals have greater room for improvement as a function of training. This is further supported by the skill learning curve observed in the Lee et al. study for individuals that are initially low performers. Individuals that begin training at a lower overall performance level experience the most significant gains in skill acquisition as a function of training strategy, compared to those that start as higher performers (Boot et al., 2010; Lee et al., in review).

We predict that our participants will have a lower baseline performance level than that observed in the Israeli sample or any other Space Fortress sample to date. Based on this evidence, it is feasible that we could see similar transfer effects to those reported by Gopher et al. Similar to the factor analysis results reported in the Israeli pilot sample, our patients also experience processing speed deficits. To reduce possible complications in
learning associated with these implicit deficits, we will be implementing the HVT training method described by Lee et al to introduce training incrementally. Based on the previous literature describing marked deficits in information processing during learning, this approach is the most logical to exploit learning gains in the MS population. It is likely that the FET approach would be too cognitively overwhelming for participants and also could introduce confounding cognitive fatigue. By breaking down the task during the initial learning phase, we are enhancing the likelihood of our participants to learn at a greater depth as well as speed.

Summary

Multiple sclerosis is a disease of the CNS that results in marked physical and cognitive impairments including deficits in attention, processing speed, executive functioning, memory and learning. Existing cognitive rehabilitation literature is scarce and somewhat inconclusive. Those studies that have been successful support a non-specific comprehensive approach to training that focuses on improvements across multiple cognitive domains. Previous research with computer-assisted cognitive training approaches in elderly populations as well as healthy younger adults supports the proposed video game training program for enhanced cognitive skills (Basak et al., 2008; Gopher et al., 1994). We propose an 8-week intervention utilizing the Space Fortress game to promote learning and complex skill acquisition as well as training transfer associated with cognitive improvement as measured by the Brief Repeatable Battery. Based on previous literature utilizing the Space Fortress game, in this study, we will investigate if a hybrid-variable priority training program will result in enhanced learning rates in
individuals with MS. This training paradigm breaks down skill acquisition into component skills before later incorporating them into the context of the full game. Utilizing this approach targeted toward the cognitive deficits commonly seen throughout the MS disease course, we predict both acquisition of skills specific to the Space Fortress game, as well as transfer to broad cognitive domains as measured by our neuropsychological battery. This transfer of skill would support the efficacy of the Space Fortress game as a feasible rehabilitation tool for cognitive deficits in MS.

**Specific Aims**

The primary objective of this study was to conduct an eight-week randomized controlled trial investigating the effects of computerized video game training on cognition in individuals with relapsing-remitting multiple sclerosis (RRMS). This project was implemented using the video game Space Fortress as a training tool (Mane & Donchin, 1989). The game was developed by cognitive psychologists to study complex skill acquisition in healthy younger adults. This particular video game approach is theoretically efficacious based on the previous literature that supports the retraining of learning strategies in multiple sclerosis (Flavia et al, 2010). Space Fortress incorporates challenging motor, memory, executive function, and visual/attention components, many of which were taken directly from the cognitive psychology literature. As part of a complex and difficult training environment, these cognitive components were combined to provide the ideal learning platform for improving impaired cognitive abilities in this population.
While much of the previous cognitive training literature for MS patients is specific to separate cognitive domains, the unique aspects of the Space Fortress game targeted multiple cognitive domains both independently and in combination. The purpose of this pilot study was to examine the utility of the Space Fortress game as a novel intervention to improve cognition in individuals with MS. The specific study aims include:

1) Determine if the eight-week cognitive training program improved game play scores for individuals with MS, relative to a no-contact control group. This included an evaluation of each sub-score across the length of the intervention as compared to the no-contact controls. Our hypothesis predicted a greater improvement of game play scores over the course of the intervention in the experimental group as compared to participants in the control group.

2) Determine if the cognitive training intervention elicited cognitive performance improvements within the domains of attention, memory and executive functioning relative to participants in a no-contact control group. Our hypotheses predicted that individuals within the experimental group will show significant improvement on the tasks that comprise Rao’s Brief Repeatable Battery from pre to post assessment (Rao et al., 1990). We further predicted that those cognitive improvements identified in the experimental group will be significantly greater than those observed in the no-contact control group.

3) Determine if the cognitive training intervention elicited improvement of fine motor skills. We predicted that individuals in the cognitive training groups
will show significantly faster times from pre to post assessment on the 9-hole-
peg test as compared to individuals in our wait-list control group.
Chapter 2

Methods

Study Design and Participant Characteristics

We conducted a single-blind intervention, comparing the effectiveness of a hybrid-variable priority training strategy, relative to a waitlist control group for acquisition of complex skills, and transfer to tasks of cognitive functioning and motor performance. Eligible participants were randomized to either an 8-week training group, or minimal contact wait-list control group. Assessments on skill acquisition were conducted pre-training, four weeks into the training, and post-training. Assessment of neuropsychological performance was completed pre- and post-training.

The completed study involved 26 individuals with a clinically definite diagnosis of relapsing-remitting multiple sclerosis. An apriori power analysis was conducted on the group x time interaction data obtained from Lee et al. (2012), based on the skill acquisition level attained by younger adults in a similar 30-hour training program. Evidence from the previous study by Lee and colleagues suggested an effect size of 0.26 (a large effect by Cohen’s division) for the time x group interaction. Based on this effect size, and a significance level of alpha = 0.05, n=14 for each group would yield an estimated power of 0.80 for the group x time interaction of a repeated measures ANOVA.
of Total Score. Participants were selected based on apriori inclusionary criteria including 20/40 visual acuity or better, dominant right-handedness as measured by the Edinburgh Handedness Inventory (Oldfield, 1971), absence of depression as measured by a score of less than 18 on the Beck Depression Inventory (Beck et al., 1993), absence of relapse and corticosteroid use for the last 30 days, between 30-59 years of age, a score higher than 23 on the Mini Mental Status Examination (Folstein et al., 1975), less than 4 hours / week of video game usage, absence of any other neurological or psychological disorders, and a score greater than 1 on the Expanded Disability Status Scale (EDSS; Kurtzke et al., 1983). Consent to collect protected health information was obtained from every participant to verify diagnosis and criteria used, disease duration, and current medications. In addition, a MS neurologist conducted pre- and post-training assessments of EDSS on each of the participants. The Ohio State University Institutional Review Board approved the study and all participants provided informed consent. Table 2 provides demographic and clinical characteristics for both groups of participants.

Recruitment and Screening Session

Individuals with RRMS were recruited from the MS center at The Ohio State University, the North American Research Committee on Multiple Sclerosis (NARCOMS), Research Match (researchmatch.org), promotional flyers, and advertisements in the local media. An incentive of $8 / hour of participation, and free parking was provided to encourage study involvement and compensate individuals for their time and efforts. The Ohio State Institutional Review Board approved all recruitment materials. Those individuals that exhibited an interest in study participation
were asked to contact the laboratory via phone or email. Upon first contact, each individual was screened by phone, to ensure study eligibility at that time.

The screening session employed an IRB-approved written script to gather demographic and disease information. A waiver of consent document was approved for this process, and all protected health information was stored on a locked computer database within the secure lab space. During this screening, participants provided demographic information on age, gender, education, and ethnicity. In addition, current medication usage, diagnosis, duration of illness, psychiatric and neurological history, current health status, and video game usage was also acquired over the phone to ensure that participants met basic eligibility criteria. Those participants successfully completing the phone screening were invited to the laboratory for the pre-training sessions.

Pre-Randomization and Post-Training Assessments

Each participant underwent two pre-randomization and post-training assessments, respectively, resulting in a total of four assessments throughout the duration of their study participation. The first assessment was conducted to collect all necessary inclusionary and exclusionary criteria that could not be completed during the phone screening process, and to gather pre-training game play data for later skill acquisition comparisons. This session included the administration of the Mini Mental Status Examination (Folstein et al. 1975) and the Beck Depression Inventory. A MS neurologist also administered the Expanded Disability Status Scale to each participant, followed by the administration of the Multiple Sclerosis Functional Composite (MSFC) to determine overall disease impact. The MSFC provides a more comprehensive, objective assessment
of disease severity, with the inclusion of cognitive and motor tasks, as compared to the physical examination and self-report that comprises the EDSS. Those tasks that comprise the MSFC are:

- Timed 25-foot walk test: This was a measure of motor coordination and walking abilities, a common source of disability in the RRMS population. Participants were asked to walk 25 ft. as quickly as possible without running. This was completed in two trials that were then averaged for analysis. The primary outcome measure was the average of how long it takes each participant to complete the task in both trials.

- 9 Hole Peg Test: This was an additional measure of motor coordination, along with motor processing speed, and dexterity. Each individual was given a set of 9 pegs and an apparatus with nine matching holes. Participants were instructed to pick up one peg at a time and place them in the holes on the board as quickly as possible. They were then instructed to remove the pegs, without pausing, as quickly as possible. Participants completed this task using their dominant hand (right hand) and non-dominant hand (left hand) across two trials for each hand. The primary outcome measure was the average of completion time for each individual, averaged across both trials for each hand.

- Paced Auditory Serial Addition Test (PASAT), 3 second condition: This task was an assessment of processing speed, working memory, and rudimentary mathematics. Participants were presented with numbers auditorily through a recording. Each individual was instructed to add the currently presented number to the number presented in the previous trial and report the sum out loud. To counteract practice effects, the score for this measure was taken from Rao’s Brief Repeatable Battery, in which the PASAT was also administered.
This first assessment also included an introduction to the space fortress game, with the intent of collecting pre-training data for later comparison of skill acquisition throughout the training-period in both study groups. Each participant was first shown a 15-minute introductory video of the space fortress game, outlining all rules, tips for success, and how to handle the joystick and mouse controls throughout gameplay. This video was followed by a 5-minute summary video highlighting the most important aspects of game play. To ensure each participant understood the rules governing the space fortress game, and controls necessary for game play, a 15-question quiz was administered directly after the instructional videos. Any questions that the participant missed were answered and clarified to the satisfaction of the experimenter. Participants then completed six, full emphasis games, totaling approximately 20 minutes of exposure. The last three games of this session were used for data analysis purposes to represent the time 1 data point.

After inclusion in the study was determined at the first testing session, a second neuropsychological assessment session was conducted to establish a cognitive baseline for each participant, consisting of paper and pencil, as well as computerized tasks. A baseline measure of intelligence using the Wechsler Test of Adult Reading (WTAR) was also collected during the course of the second assessment. Rao’s Brief Repeatable Battery was also administered to assess a variety of cognitive domains including attention, memory, processing speed, working memory, and executive functioning. The tests that comprise this battery included:
• **Selective Reminding Task:** This task was an assessment of short and long-term memory storage for verbal stimuli. The SRT involved reading a list of 12 words and asking each participant to recall as many words as possible. After recall, they were reminded of words that were not recalled from the list of twelve in that particular trial and asked to repeat the entire list of 12 words from memory again. This procedure was continued for 6 trials or until the participant recalled all 12 words. Delayed recall of all 12 words was administered later in the battery, requiring each participant to repeat the list of 12 words from memory, after an approximate time delay of 15 minutes, without any cues from the research assistant. The primary outcome measure was the number of trials required for each participant to learn as many words as possible as well as the number of words recalled after a delay. This was assessed by two main dependent variables; Long Term Storage (LTS) identified by two consecutive recalls of the word and Consistent Long Term Retrieval (CLTR) or a word that is in LTS and is recalled on all subsequent trials.

• **Paced Auditory Serial Addition Test (PASAT):** This task is an assessment of working memory functioning, processing speed, and simple arithmetic. Participants were auditorily presented with digits at the rate of 2 seconds/digit or 3 seconds/digit in two separate conditions. Participants were instructed to add each number heard to the number previously heard and report the sum out loud. Accuracy of response was the primary outcome measure, calculated separately for 2 and 3-second conditions. The PASAT assessment was only administered once at pre and post training time-points, although it was included in the BRB and MSFC
analyses. Data from one administration was used for both assessments to reduce practice effects.

- **Word List Generation Task**: This is a task of verbal fluency and executive functioning. Each participant was provided with a letter of the alphabet, and instructed to generate as many words as they could think of in 60 seconds that began with that letter. This was repeated two additional times with different letters for a total of three trials. The number of correct generated responses across all three trials was our primary outcome measure.

- **10/36 Spatial Recall Task**: This is a task of spatial working memory and long-term spatial memory. A checkerboard was placed in front of each participant for 10 seconds with a particular pattern of pieces on display. This display was subsequently removed, and the participant was asked to replicate the provided pattern from memory on an empty checkerboard. Two additional trials of the same pattern were administered, or until the participant attained a perfect score. After a 15-minute delay, the participant was asked to recall the same design again to test delayed recall accuracy, without an additional presentation of the original checkerboard stimulus. Accuracy of recall was the primary outcome variable.

- **Oral Symbol Digit Modalities Test**: This is a task of processing speed with some elements of working memory necessary for completion. Participants were presented with a series of geometric shapes that were assigned numbers 1-9 at the in a key at the top of the page. The bottom contained only geometric shapes, repeated several times in random order, with a blank space below. Participants were asked to verbalize the numbers from the key at the top of the page that
correspond to the geometric shapes presented at the bottom, as quickly as possible. The experimenter recorded answers for the participant to remove variability associated with motoric processing speed impairments, and produce a purer measure of cognitive processing speed. While rate of speed impairments could also affect the subtest outcome, these are less common at early disease stages, and are difficult to discern from cognitive processing speed deficits.

Participants were given 90 seconds to complete as many of the symbol-digit pairings as they could with directions to complete as many trials “as quickly, but as accurately as possible.” The number of correctly generated responses as the primary outcome measure.

Following the 8-week cognitive training period, the two sessions comprising the pretest assessments were repeated a second time to obtain post-test data for comparison. The post-training assessments were administered within a two-week time window of each participant’s completion of the 8-week cognitive training or wait-list period. A detailed flow chart of the study procedure is provided in Figure 1.

**Randomization and Blinding**

After participants were determined eligible based on both pre-randomization assessment sessions, they were randomized to either the cognitive training group or a wait-listed control group, using a random number generator. A list of 30 random numbers were generated prior to the start of the study and kept in a locked excel file. As individuals completed the assessments, their names were added to this list in order, to ensure complete randomization. Those participants in the wait-list control group were
informed of their future ability to participate in the cognitive training after the 12 weeks of data collection had commenced. However, there were no individuals that accepted this invitation throughout the course of the study. Admission to the study was completed on a rolling basis as participants became available for randomization.

All investigators and key personnel that performed assessments were blinded to group assignment except for the study coordinator and research assistants administering the training sessions. Participants that became aware of other individuals participating in the study were asked not to share the details of their group assignment. Key personnel that became aware of an individual’s group assignment were prohibited from completing any further assessments with that participant. Participants were encouraged to remain within their testing rooms at all times, and otherwise escorted by an unblinded personnel to ensure their group assignment remained blinded to the assessors. Training and testing rooms, while housed within the laboratory, were completely closed off to outside personnel, and identified during testing sessions as occupied. All computer containing group assignment were kept in one physical location within the laboratory and password protected at all times.

_Space Fortress Game:_

In this study, we employed the video game Space Fortress designed by cognitive psychologists (Mané & Donchin, 1989) to study skill acquisition. Space fortress required players to navigate their ship with precise control through a frictionless environment using a joystick. A depiction of the space fortress environment is provided in Figure 3. In
order for players to stop or reverse the ship, they were required to rotate it in the opposite
direction and apply a thrust to counteract their current trajectory, thus, making ship
control a very demanding and challenging task. The main goal of the game was for
players to destroy the space fortress (smaller hexagon in the middle of the screen) as
many times as possible while avoiding damage to their own ship (player ship). To destroy
the fortress, players were required to hit it with missiles from their own ship (arrow
shape), by aiming their ship and firing via a button on the top of the joystick. For the
space fortress to be destroyed, it had to first be made vulnerable by hitting it with 10
preliminary missiles. After the tenth hit, the player was directed to fire a rapid double
shot, or a two shots within 250 ms of each other, for the space fortress to be destroyed. If
the player fired a double shot before the space fortress had reached full vulnerability (10
preliminary hits), the vulnerability count was reset to zero.

During this time, the space fortress was also rotating and actively firing at the
player’s ship (fortress shot). After the player’s ship had been hit four times by the space
fortress, it was destroyed, and their vulnerability was reset to 0. Every time the ship was
destroyed, there was also an accompanying deduction in points. While battling the space
fortress, mines were also regularly appearing on the screen that the player’s ship was
likely to come into contact with, and the player was incapacitated from damaging the
space fortress while mines were present on the screen. Each mine that appeared was
associated with a letter displayed in the control panel at the bottom of the player’s screen.
Before each game, the player was presented with three letters that represent “foe” mines.
When the foe mines would subsequently appear in the following game, the player was
instructed to label them as such by double clicking the mouse. Only then could the player
destroy the mine and receive points. Incorrectly identifying mines would have negative consequences so players were urged to be careful to remember which letters represent foe mines. If a foe mine was not identified, it resulted in a loss of points on multiple sub-scores, as well as the overall total score.

In addition to these tasks, there was also a constant monitoring task embedded within the game. Below the space fortress (smaller hexagon) was a resource stream of different symbols. Whenever two dollar signs were presented in direct succession, the player was directed to click a button on the mouse to receive either extra missiles or extra points. However, if the participant was not monitoring effectively and identified the first dollar sign instead of the second, they lost the opportunity to collect a bonus when the second dollar sign did appear.

The total score was determined based on participant’s overall performance on the Space Fortress game. The total score was comprised of four sub-scores: control, points, speed and velocity. Control scores were awarded when players could keep their ship within the two hexagons on the screen. Flying the ship outside of these hexagons or leaving the screen completely detracted from the Control score. Point scores were awarded when the player shot and destroyed the space fortress, effectively. Conversely, points were subtracted when the space fortress damaged the player’s ship. The speed sub-score was related to how quickly participants deal with mines. A greater score was achieved for a quick reaction to mines on the screen, or detracted from for a slow reaction or ignoring the mine all together. The velocity sub-score rewarded participants for flying their ship slowly and punished for flying at high-speeds.
Experimental and Control Group Protocols:

All participants meeting the inclusionary criteria were randomized to either a hybrid-variable priority group or a wait-listed control group. For the period of the intervention, participants in both groups were asked to notify the experimenters of any sudden adjustments in their medical therapies or significant lifestyle changes and stressors. Those participants that did suffer a relapse during the course of the intervention, were referred to their primary care neurologist, and strongly recommended to withdraw from the study to ensure their own safety and the integrity of the study. Along those same lines, any participant that began corticosteroid therapy during the course of the intervention were encouraged to withdraw due to the cognitive implications of corticosteroid use on executive functioning. All participants that suffered a relapse or required corticosteroid therapy were unable to comply with these guidelines and were not included in the final sample. Participation in the study also required each individual to complete the training or wait-list control period within a 10-week period, at the most. Those participants that could not comply with this deadline were omitted from further data analysis, due to confounding variance from a differential training or wait-list time course.

Hybrid-Variable Priority Training Strategy (Experimental Group): For the purpose of the current study, we utilized the hybrid-variable priority training strategy (HVT) first proposed by Gopher et al. (1994), and later re-employed by Lee et al. (2012) and Prakash et al. (2011) to examine the effects of strategy on skill acquisition. In the HVT strategy, for the first 10 sessions, study group participants practiced the part-task training. This
learning approach divided the space fortress game into 14 part tasks, each about two minutes long that focused on different aspects of the game. For instance, one part task focused just on bonus detection, while another focused only on mine detection. Multiple part tasks were devoted to ship flight control. In these part-task training sessions, the participant first completed 3 full-emphasis games, or games that are not altered from the original space fortress format. After this, they completed all 14 part-task games and, finally, another 3 full emphasis games. Full emphasis games were necessary for determining the learning curve of each participant during training.

The next 10 sessions consisted of a variable priority training (VPT) strategy. This strategy highlighted different aspects of the full emphasis game. For example, for one game, the participant were told to emphasize the control score, or try to obtain the highest control score possible with less emphasis on other scores. In VPT sessions, participants completed 3 full emphasis games first, followed by 6 variable priority games, with a varying order emphasizing points, control, speed, velocity and total score. Variable priority emphasis order was counterbalanced for each participant across all 10 sessions. VPT training sessions ended with another 3 full-emphasis games. Further details of the part-task and variable priority training sessions can be found in Table 1.

Wait-listed Control Group: Individuals in the control group were contacted every two weeks to ensure they were in good health and complying with the guidelines of the study. We asked that during this training process, the wait-list control group refrain from participating in any other experimental trials to limit the effect of additional confounding variables. Participants in the wait-list control group were also required to attend two
training sessions at week 4 and week 8, respectively, to obtain comparison game-play data for skill acquisition analysis. Baseline space fortress abilities were initially ascertained using 6 full emphasis games at the first assessment session. Previous research has shown that learning gains can appear as early as 10 hours into training (Lee et al., 2012). Therefore, we also had the control group complete a mid-point training session some time during week 4 of the intervention period, after the experimental group had finished approximately 10 hours of training. These training sessions consisted of 6 full-emphasis games. The participant first played 3 full-emphasis games, then a distracter task for 34 minutes. This distracter task was necessary to ensure equal fatigue levels across control and study groups for the last 3 full emphasis games. After completing this 34-minute task, the participant were then asked complete an additional 3 full-emphasis games. A visual depiction of the intervention procedures can be found in Figure 1.

Adherence and Attrition Rates

Forty-eight individuals with RRMS were recruited, in total, from the aforementioned sites and materials. A flowchart of study adherence and attrition can be found in Figure 2, visually depicting the number of individuals who were lost at each stage of the screening, assessment, and intervention process. Sixteen individuals were excluded from study participation during the assessment process due to exclusionary criteria based on Beck Depression Inventory scores (10 individuals), EDSS scores (2 individuals), relapse during the assessment process (1 individual), and MMSE scores (1 individual). Two individuals passed the phone screening, and were scheduled for subsequent appointments, but chose not to attend any of their assessment sessions.
Four participants were lost during the course of the intervention process. Reasons for this attrition from the training group were circumscribed to a relapse occurrence (2 individuals). Two individuals were lost from the waitlist control group due to issues with scheduling and time commitments. Two additional individuals completed the training period within 12 weeks and the post-training session, but were excluded from final analyses based on prolonged training duration (more than 10 weeks). This resulted in 8% attrition from the study, after randomization.

Data Analysis

1. Statistical analysis of Space Fortress Data

The Statistical Package for the Social Sciences (SPSS) was employed for all data analysis. Statistical significance was based on an apriori determined $p$-value of 0.05. Each data point for analysis of Space Fortress performance was based on the average score of the last 3 full emphasis games of each session, and was collected for the total score, in addition to all four sub-scores. There were three time points for each individual representing pre-training, week 4, and week 8 of the intervention. All data collected from game play was tested for multivariate normality of ANOVA residuals, multivariate outliers. Skewness and kurtosis were determined based on two times the standard error of the statistic. An independent sample’s $t$-test was conducted between groups to detect any significant differences in EDSS, age, education, IQ, disease duration, fatigue, depression scores, and initial performance level on game-play. A chi-square test of significant differences was utilized for categorical variables, including gender, to ensure no significant differences existed across groups. None of these variables were significantly
different between the two groups at baseline, and were thus not used as covariates in subsequent analyses. The first hypothesis was tested by conducting a repeated-measures ANOVA for total score; the composite of all 4 sub-scores, using the 3 time points from the training group and control group scores with time (pre-training, week 4, and week 8) as the within-subject factor and group (training, control) as the between-subject factor. Significance was based on the $F$-test of the group x time interaction. Final results are based on the $F$-test with all significant outliers removed when necessary. To further probe for the independent effects of each sub-score on the outcome of the Total score ANOVA, four additional single, repeated-measures ANOVAs were completed on each of the four sub-scores, with significance based on the $F$-value of the time x group interaction. We inspected each of analyses for violations of sphericity using the Mauchly’s test of significance, and Greenhouse-Geisser corrections were applied wherever violations of the hypothesized and observed variance/co-variance patterns was noted.

2. Statistical Analyses of Neuropsychological Data

All behavioral data was tested for multivariate normality of ANOVA residuals and multivariate outliers. An independent sample $t$-test for continuous variables and chi-square for categorical variables were used to verify the presence of any significant differences in confounding variables or initial cognitive performance level, as mentioned above. No significant differences were detected, and these were not used as covariates in subsequent analyses. The second hypothesis was tested by comparing the changes in cognitive data on all 5 subtests that comprise the Brief Repeatable Battery, pre- and post-training for both study groups. Data at both time points was considered normative for this
population by a value within 1.5 standard deviations of the norms provided for each subtest (Boringa et al., 2001). The nine dependent variables that were collected through these tasks were z-standardized, and then a composite score was created for the pre- and the post-training sessions. The pre-training composite score, comprising of pre-training data on the 2-second PASAT condition, the 3-second PASAT condition, long-term storage from the SRT, consecutive long-term retrieval from the SRT, delayed recall from the SRT, total correct on the SDMT, total correct on the 10/36 spatial recall, total correct on the delayed 10/36 spatial recall, and total words generated from the WLGT was compared to the post-training composite score using a repeated-measures ANOVA. In this analysis, time (pre-training, post-training) was the within-subject factor and group (training, control) as the between-subject factor to determine the overall transfer effect of the intervention on our dependent variable, executive functioning and attention as measured by the BRB. Significance was based on the time x group interaction of the $F$-test. Exploratory analyses, probing for the effect of the training on each of the sub-components of the BRB were additionally conducted by employing repeated-measures ANOVA for each of the 9 sub-components.

The third hypothesis was tested by comparing change in performance on the 9-hole peg test in the two groups. This was completed by first creating a composite score for each individual by averaging the two administered trials for each hand. These averaged scores were tested for multivariate normality for residuals, and multivariate outlier detection. All variables of non-interest were tested for significant differences at time 1, revealing non-significant effects including initial 9-hole-peg performance, negating the necessity of an analysis of covariance. An overall, repeated-measures
ANOVA was completed using both dominant and non-dominant hand averages, with time as the within-subjects factor and group as the between-subjects factor. Significance was based on the $F$-value of the repeated-measures ANOVA.
Chapter 3

Results

Demographics

Table 2 displays group level statistics of demographic characteristics. Individual samples t-tests were performed to ensure no statistically significant differences existed between the two groups. Given the lack of statistically significant differences between the two groups at baseline, demographic variables were not included as covariates in the group level analyses. The final N was 26, with 14 of those participants completing the wait-list control condition and 12 completing the training condition.

Space Fortress Results

Table 3 displays the repeated-measures ANOVA results for the five sub-scores of the space fortress game. In support of our first hypothesis, the test of Total Score, a composite of all four sub-scores, was significant at $F(1.29,24) = 7.57, p < 0.01, \eta^2 = 0.24$, signifying greater skill acquisition in our training group as compared to our control. Closer examination of Figure 4 reveals that higher scores in the training group are driving this effect, and the difference between groups was significant beginning at week 4 ($t(24) = 2.12, p < 0.05$) and continuing through to week 8 ($t(24) = 2.31, p < 0.05$).
Further analysis of sub-score changes helped to elucidate which improvements specific to the space fortress game were driving overall skill acquisition, as evidenced by a significant change in Total score. A repeated-measures ANOVA of the Points sub-score was significant, $F (1.63,24) = 5.24, p < 0.01, \eta^2 = 0.19$, signifying significant learning from pre-training to week 8 on those skills necessary to evade the space fortress, while subsequently lowering its vulnerability. The difference in points sub-score between the training and wait-list control group, in contrast to the total score, were not significant at week 4 ($t(13.96) = 0.33, p > 0.05$), but were significant, with the training participants performing better than the control participants at week 8 ($t(13.12) = 3.05, p < 0.01$).

Results of the repeated measures ANOVA for the Control sub-score illustrated an overall skill acquisition gain in the training group, as compared to wait-listed controls, ($F (2,24) = 11.30, p < 0.01, \eta^2 = 0.32$). In contrast to the points sub-score, there was evidence of trending effects of training on the Control sub-score at week 4($t(19.2) = 1.89, p < 0.1$) and significant effects at week 8 ($t(24) = 3.51, p < 0.01$) respectively. The control sub-score measures a participant’s ability to keep the ship on the screen and within the hexagon boundaries, relying on more basic cognitive processes such as mental and motoric processing speed, and dexterity with the joystick.

The Speed sub-score proved similarly significant after eight weeks of training ($F (2,24) = 3.85, p < 0.01, \eta^2 = 0.27$). A break down of this effect at week 4 and week 8 time points illustrated a significant effect ($t(24) = 4.1, p < 0.01$) at both time points ($t(24) = 3.51, p < 0.01$), respectively. The speed score is an analysis of mine control and a test of divided attention and monitoring abilities.
An analysis of the Velocity sub-score, or the player’s ability to fly the ship at low speeds, was significant after eight weeks of training, relative to pre-training ($F(1.51, 24) = 5.07, p < 0.05, \eta^2 = 0.17$). Further analysis of each time point revealed no evidence for improvement at week 4 ($t(18.54) = 1.61, p > 0.1$), but a significant effect of training at week 8 ($t(19.52) = 2.32, p < 0.05$).

Brief Repeatable Battery Results

Table 4 displays the results of the omnibus analysis of all nine sub-scores that comprise Rao’s Brief Repeatable Battery, as well as the individual analysis of each sub-component. The overall test of BRB performance revealed a null effect of training, $F(1, 24) = 0.02, p > 0.1, \eta^2 = 0.00$, signifying no change in overall cognitive performance as a function of the intervention. A graphical depiction of the overall effect can be found in Figure 5. While the overall ANOVA was non-significant, we conducted additional analyses to determine the specific effects of the training on sub-components of the BRB. In here, we performed 9 repeated-measures ANOVA, and a Bonferroni corrected p-value of 0.005 was used to determine statistical significance.

We did not find an effect of the training program on general working memory performance as evidenced by scores on both versions of the PASAT (PASAT 2s. $F(1, 24) = 0.001, p > 0.1, \eta^2 = 0.00$, PASAT 3s. $F(1, 24) = 0.20, p > 0.1, \eta^2 = 0.008$). An analysis of the Selective Reminding Task revealed a change in favor of the control group on measures of long-term storage ($F(1, 24) = 4.14, p = 0.05, \eta^2 = 0.15$), and consecutive long-term retrieval ($F(1, 24) = 3.98, p = 0.06, \eta^2 = 0.14$) However, both these results did
not survive correction for multiple comparisons. There was no effect of training on the delayed recall of the SRT ($F(1, 24) = 2.33, p > 0.1, \eta^2 = 0.09$).

There also appeared to be a null effect of the intervention on general processing speed performance as evidenced by the Oral Symbol Digit Modalities Test ($F(1,24) = 0.26, p > 0.1, \eta^2 = 0.01$). Results of the 10/36 spatial recall exhibited a significant effect, in favor of the training group ($F(1,24) = 8.58, p = 0.007, \eta^2 = 0.26$); however, this effect also failed to survive correction for multiple comparison. A delayed version of the 10/36 spatial recall also exhibited no effect of transfer to measures of long-term spatial memory ($F(1,24) = 0.40, p > 0.1, \eta^2 = 0.03$). Higher-order functions, as measured by the verbal fluency demands of the word-list generation task, also exhibited non-significant results ($F(1,24) = 1.14, p > 0.1, \eta^2 = 0.05$). Visual depictions of each of these results can be found in Figure 5.

9-Hole Peg Test Results

Table 5 displays the omnibus and independent handedness transfer results to the 9-Hole-Peg test. Results of the omnibus repeated measures ANOVA reveal a non-significant effect of the intervention on the overall measure of manual dexterity on both hands ($F(1,24) = 2.68, p > 0.1, \eta^2 = 0.10$). A graphical representation of the omnibus effect is included in Figure 6.
Chapter 4

Discussion

The implications of a feasible and easily disseminable cognitive rehabilitation strategy for reducing executive functioning and attention deficits with concurrent improvements in overall quality of life has become a topic of great interest to the MS community. Those interventions that have targeted memory and learning impairments have been successful at improving memory techniques such as elaborative rehearsal and mnemonic memory strategies to produce significant transfer effects to broader measures of memory performance and subjective ratings of memory improvement (Chiaravalloti et al., 2005; Mendozzi et al., 1998). However, options to ameliorate executive functioning and attentional impairments have elicited mixed results, with few options providing broad transfer effects to multiple domains of functioning (Solari et al., 2004; Plohman et al., 1998; Vogt et al., 2009). In this study, we proposed rehabilitation from a bottom-up theoretical perspective, using a hybrid variable priority training approach employing the Space Fortress video game platform, engineered specifically to train sub-components of higher-order executive functioning. The HVT strategy, combining both part-task training and variable priority training, focuses initially on training in isolation, those processes that play a supportive role in executive functioning, such as processing speed, attention, and working memory storage (part-task training) and then allowing for sub-component
integration within the larger task, while still limiting overall demand. Based on Green and Bavelier’s theory of probabilistic inference (Green et al., 2010), we proposed that a bottom-up learning perspective would help improve processing speed, attention, and working memory capacity early in the intervention, to support these cognitive components as building blocks for later skill acquisition and transfer to broader cognitive domains (Green et al, 2010; See Janssen & Prakash, in review, for a review of this theoretical model).

The results of our eight-week space fortress training intervention appear to support the bottom-up skill acquisition perspective, despite negligible effects of cognitive transfer. Specifically, we saw an improvement in total game score as evidenced by a significant time x group interaction in our repeated-measures model. This substantiates previous findings of successful learning and skill acquisition in the RRMS population (See Rao et al., 2004 for review; Amann, 2011). More recent studies of skill acquisition have observed changes in the functional neural correlates of skill learning before cognitive impairment is detectable (Amann et al., 2011). Therefore, it is possible that changes in the functional reorganization of the brain have also been affected, as a function of the training intervention, before objective behavioral change could be detected. It is also plausible that behavioral changes in broader domains of cognition will follow structural changes, as they have in so many cases of impairment progression (Amato et al., 2007 & 2010; Penner et al., 2003). Thus, a significant effect of skill acquisition in the space fortress environment could represent the first necessary steps for behavioral changes in transfer effects, once adequate skill level is achieved. Additional
improvements to the current training platform would be necessary to determine if this would indeed be the case.

Further analysis of sub-component scores revealed a differential improvement on targeted measures of skill acquisition within the larger space fortress game. Our results indicated a significant change on all sub-scores measured as part of the space fortress training intervention. The points sub-score, a reflection of the number of times a player can destroy the fortress, and avoid being destroyed, in addition to collecting bonuses, is tightly coupled to the overall purpose of the game. The space fortress is situated in the middle of the screen, and ship damage or destruction can impede a player’s ability to complete any other tasks, as measured by additional sub-scores. Thus, it is likely that participants would have focused on this sub-score throughout their game play due to its close association with the superordinate goal of the game and the integral role it plays in subsequent skill acquisition on other sub-scores. Given the importance of this sub-score to the overall purpose of the game, our results provide evidence of significant learning as related to this sub-score through the course of the training. The speed sub-score is a reflection of the player’s ability to deal efficiently and effectively with secondary mine control as they appear on the screen. A letter appearing at the beginning of the game identifies each mine, and the player must be able to label mines based on their ability to hold those letters in short-term memory storage. Thus, skill acquisition, as measured by the speed sub-score, represents a player’s ability to both multi-task with secondary goals, and maintain a three-letter string in short-term memory storage throughout game play. Participants in the training group, in fact, did show significant improvements on the
speed sub-score, thus possibly suggesting both an enhancement of multi-tasking and working memory capacities as a function of the training.

The control sub-score represents a player’s ability to keep their ship within the two hexagons presented on the screen, and fly in a clockwise direction. This requires manual dexterity and small, incremental movements that are difficult for individuals with multiple sclerosis to execute (Benedict et al., 2011). Similarly, the velocity sub-score also requires incremental joystick movements to keep the player’s ship flying at a low velocity throughout game play. This can be accomplished in two separate avenues; either by maintaining a low velocity from the beginning of game play by using subtle joystick movements, or by slowing down the player’s ship after it has reached a high velocity as a result of poor joystick control using incremental, slight joystick movements. Both measures of control and velocity equate to manual joystick maneuvering changes as a function of the training program, and the improvement in both these scores as a function of training suggests the possibility of enhanced motor control at least in the environment of the SF game.

The results of the nine-hole-peg test were utilized to further elucidate the broad transfer of joystick maneuvering changes to measures of manual dexterity. However, despite changes in motor control on the SF game, we did not find evidence for transfer of these skills to fine motor control, as assessed by this measure. It appears that the current intervention was not sufficient to produce manual dexterity changes outside of the space fortress environment. As the first computerized video game rehabilitation program to apply the space fortress paradigm, little can be said conclusively about why manual dexterity transfer from joystick maneuverability to broader measures of motor processing
and fine motor skills did not occur. To date, there have been no published studies of the effects of space fortress on manual dexterity, although there have been many gains in the field of robotic training for upper extremity and dexterity rehabilitation in the multiple sclerosis population (See Brochard et al., 2010 for a review). Future directions for this project could evaluate the association between current robotics research and video game implementation to provide a fully rounded physical and cognitive intervention to improve dexterity and motor functioning in addition to ameliorating cognitive deficits.

One of the secondary aims of this study was to investigate the transfer effects of cognitive training to broader measures of executive functioning and attentional decline associated with the RRMS disease course. Our results suggested that the current training program did not result in significant improvements on those tasks that comprise the Brief Repeatable Battery, and encompass a wide array of cognitive functioning demands (Rao et al., 1993). This result was surprising, especially given previous investigations of significant transfer effects in both young adult populations (Lee et al. 2012, Chiappe et al., 2013) and in older adults (Stern et al., 2011). Lee and colleagues, employing the HVT strategy found transfer effects on tasks of working memory and selective attention, cognitive domains that were closely aligned with the SF video game. While they failed to find broad transfer effects, a more recent implementation of the SF intervention in young adults utilized a training regimen of 50 hours, more than twice that implemented in the current study (Chiappe et al., 2013). The results indicated a significant effect of training to the secondary tasks of the Multi-Attribute Tasks Battery, assessing domains of multi-tasking, decision-making and divided attention in a computer-based, simulation environment. Similarly, in a study by Stern et al. (2011) with older adults, the authors
found that 36 hours of VPT training, over the course of 12 months, resulted in significant
transfer to letter-number sequencing, a measure of working memory and processing
speed as part of the Wechsler Adult Intelligence Scale, Fourth Edition. Thus, given these
previous investigations, we had hypothesized a significant improvement on tasks of
broader cognition in our sample of MS participants. One interpretation for a lack of such
transfer effects could be the limited gain in SF performance in our sample of MS
participants, as compared to the three studies cited above. While participants in the
experimental group showed significantly better performance than participants in the
control group, their overall performance on the SF game was still substantially lower than
participants that have been previously studied in the Lee et al. (2012), Stern et al. (2011),
and Chiappe et al., (2013) studies. While all three of these studies conducted training of
different durations, in Figure 7, we plot the total score obtained by participants in the Lee
et al. study with 20 hours of training, as well as our participants at the end of 20 hours of
training. MS individuals trained with the same HVT space fortress program, as compared
to a young adult population, fall substantially short of what could be attained in normal
game play. In other words, it is possible that RRMS individuals in our study have not
received a large enough dose of training to produce significant effects of transfer, as
evidenced by their inability to reach higher game-play scores by the end of 20 hours of
training. Future endeavors of the HVT training paradigm as a rehabilitation tool for MS-
related cognitive impairment would do well to implement a training strategy program of
at least 40 hours or greater to elicit similar effect sizes as those observed above.

Another possible explanation for the lack of transfer results observed in the
current study could be the inclusion of individuals with RRMS that did not exhibit
marked deficits in cognitive processing. Meta-analytic evidence within the MS population, illustrates the most robust and reliable results in cognitive rehabilitation programs for those individuals who were cognitively impaired at the start of training, with markedly better results for moderately to severely impaired patients (Rosti-Otajarvi & Hamalainen, 2011). Indeed, a previous investigation by Foss et al. (1989) comparing studies that show transfer effects to studies that fail to find such benefits, attributed the variance in transfer effects to differing levels of baseline cognitive processing, with ceiling effects at baseline hypothesized to underlie the failure to find significant transfer effects (Whitlock et al., 2012). In our study, we did not specifically select participants with impaired cognitive processing with the assumption that all included participants will show some processing speed decrements, and an intervention that finds transfer benefits in a general population of MS patients would show higher external validity. Future endeavors with the bottom-up focused retraining perspective, would benefit from stratifying participants based on cognitive impairment and examine the differential impact of training on cognitively impaired versus cognitively unimpaired individuals.

To our surprise, we found trending results, in favor of the control group, for both dependent variables measuring immediate recall as part of the Selective Reminding Test; the long-term storage and consistent long-term retrieval scores. The SRT, designed to differentiate between the processes involved in memory functioning, has two main dependent variables: long-term storage and consistent long-term retrieval. Participants successfully recalling a word on two consecutive trials, earn a score for that word on the measure of long-term storage, thus suggesting that an inability to recall the word on subsequent trials was largely a result of retrieval failure, rather than a failure of storage.
CLTR, however, is a measure of retrieval from long-term memory, and our results provided evidence that control participants, post-training performed better on both these measure, relative to training participants. These results, are surprising, given that the control participants did not specifically receive any training, and while we did not expect our training participants to improve on this measure of long-term retrieval, given the nature of the intervention, the improvement of control participants is perplexing, and possibly a result of practice effects with the SRT paradigm.

Finally, to examine our third hypothesis investigating the efficacy of this training program on manual dexterity, we administered the 9-hole peg test to our participants pre- and post-training. As previously mentioned, these results did not provide a significant effect of the intervention on broad measures of manual dexterity, as evidenced by the non-significant omnibus ANOVA effect. This was the first intervention to propose an effect of space fortress training on non-joystick dependent measures of manual dexterity. Several previous studies have concluded significant effects of the intervention on joystick-based measures of manual control, (Gopher et al., 1994; Chiappe et al., 2013), but have not broadened these results to non-joystick dependent measures. While the current results of our investigation are not statistically significance, further investigation into the use of the HVT training strategy and space fortress platform in reducing problems of fine motor control in this population could be warranted by a joystick dependent motor paradigm.

The lack of transfer effects observed in the current study does aid in pointing out some significant areas for improvement and future development of this rehabilitation strategy. As noted above, a longer training schedule to induce skill acquisition at or above
the level of healthy younger adults would be critical for the effectiveness of such a
computerized, bottom-up oriented training strategy in this population. We would propose
an additional 20 hours of training, to raise the total training hours to 40 over the course of
a 12 week intervention period. It would also be relevant to limit future trials to
individuals that display a significant cognitive impairment in the domains of executive
functioning and attention, specifically using the standardized, norm-based cut-offs
provided by the MACFIMS battery (Multiple Assessment of Cognitive Functioning in
Multiple Sclerosis, Benedict et al., 2006). In addition, previous research has also
provided functional neural correlates of cognitive change during computerized cognitive
retraining programs, including an association between increased activation of cerebellar
areas associated with improved executive attention (Sastria-Garriga et al., 2010). The
addition of functional neuroimaging to our study of cognitive rehabilitation could
elucidate the neural correlates of behavioral change, as well as provide evidence of
improvement before behavioral effects are elicited.

The observed behavioral transfer effects could also be improved by a larger
sample size. Due to the novelty of this training paradigm, utilized for the first time in a
clinical population, we based our apriori power analysis on game-play effects in a healthy
young adult population, rather than transfer effects in a cognitively impaired population.
Utilizing the effect sizes provided in the current analysis, and a more targeted battery of
executive functioning and attention tasks, a larger sample size with a significant degree of
cognitive impairment would be more appropriate to achieve significant transfer results,
based on the signature of RRMS cognitive deficits. Specifically, we would include in
future investigations those tasks eliciting the greatest improvement in the current
intervention to shape subsequent apriori power analyses. One task of note that would provide theoretical insight into future analyses would be the 10/36 spatial recall, eliciting the largest effect size in the hypothesized direction. An addition of subjective measures of improvement would provide additional depth and explanatory value to transfer results. Specifically, those effects that individuals perceive as beneficial to their daily lives, or subjectively improved from baseline, are the most efficacious for treatment purposes and improving overall quality of life.

Conclusions

The results of the current investigation provide support for the feasibility of an intense, cognitive training program in inducing skill acquisition in individuals with relapsing-remitting multiple sclerosis. We proposed this bottom-up training strategy based on previous research that has defined processing speed deficits as the driving force in executive functioning impairment in this population (DeLuca et al., 2004). Previous investigations of HVT and VPT training interventions with healthy young adults and older adult populations have provided significant support for this training strategy. The significant effect of the HVT strategy on skill acquisition in this sample lends support to our rehabilitation program, and feasibility to the space fortress HVT strategy as a whole in producing learning gains within the RRMS population. While limited effects of transfer to broader measures of cognition were observed, several study limitations were identified for future research endeavors including an increase in study duration, inclusion of individuals with a defined cognitive impairment profile, and a larger subject sample size. For future research, we would also propose the addition of functional and structural
neuroimaging to provide additional insights into its efficacy as a disseminable rehabilitation approach within the RRMS population.
References


sclerosis. Milwaukee, WI: Medical College of Wisconsin.


Table 1: Overview of Training Programs

**APPENDIX A:**

*Tables*

Table 1: Details of the part-task and variable priority sessions outlined in the proposal.

<table>
<thead>
<tr>
<th><strong>Part-Task Training</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Three full emphasis games</td>
</tr>
<tr>
<td>2. Slow down a ship</td>
</tr>
<tr>
<td>3. Aiming</td>
</tr>
<tr>
<td>4. Aiming and Firing</td>
</tr>
<tr>
<td>5. Navigating a ship in trajectory 1</td>
</tr>
<tr>
<td>6. Navigating a ship in trajectory 2</td>
</tr>
<tr>
<td>7. Navigating a ship in trajectory 3</td>
</tr>
<tr>
<td>8. Navigating a ship in big hexagon</td>
</tr>
<tr>
<td>9. Navigating a ship in small hexagon</td>
</tr>
<tr>
<td>10. Navigating a ship in hexagon and aiming</td>
</tr>
<tr>
<td>11. Navigating a ship in hexagon, aiming and firing</td>
</tr>
<tr>
<td>12. Navigating a ship in hexagon, aiming and firing on the shooting fortress</td>
</tr>
<tr>
<td>13. Ship control only</td>
</tr>
<tr>
<td>14. Mine control only</td>
</tr>
<tr>
<td>15. Bonus control only</td>
</tr>
<tr>
<td>16. Three full emphasis games</td>
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<table>
<thead>
<tr>
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<tr>
<td>1. Total Score Emphasis- 3 games</td>
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<tr>
<td>2. Points Score Emphasis- 2 games</td>
</tr>
<tr>
<td>3. Control Score Emphasis- 2 games</td>
</tr>
<tr>
<td>4. Velocity Score Emphasis- 2 games</td>
</tr>
<tr>
<td>5. Speed score Emphasis- 2 games</td>
</tr>
<tr>
<td>6. Total Score Emphasis- 3 games</td>
</tr>
</tbody>
</table>

Table 1: Overview of Training Programs
Table 2. A display of demographic variables means for each study group and standard deviations in parentheses. The last row of the table illustrates the results of independent samples t-test to elucidate any significant confounding variables across groups. *t*-values are displayed in the last row. **p-value<0.01, *p-value<0.05, †p-value<0.1.

***Gender was tested as a categorical variable using Pearson’s χ².
Table 3. Displays Space Fortress score results for the omnibus ANOVA test as well as each independent sub-score analysis. Mean values for pretraining (Time 1), week 4 (Time 2) and week 8 (Time 3) are presented with standard deviation values in parentheses. The last row displays the results of the $F$-test and the obtained effect size in partial $\eta^2$. **p-value<0.01, *p-value<0.05.

<table>
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<tr>
<th>Group</th>
<th>Total</th>
<th>Points</th>
<th>Control</th>
<th>Speed</th>
<th>Velocity</th>
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<td>Time 1</td>
<td>Time 2</td>
<td>Time 3</td>
<td></td>
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<td>-979.69 (537.36)</td>
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<td>-572.83 (354.04)</td>
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<td>-1255.39 (1136.07)</td>
<td>-291.89 (834.36)</td>
<td>137.22 (164.68)</td>
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<td>-280.06 (3306.84)</td>
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<td>299.81 (848.19)</td>
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<td>-819.93 (776.36)</td>
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<td>$F$-value</td>
<td>7.57**</td>
<td>5.24**</td>
<td>11.30**</td>
<td>3.85**</td>
<td>5.07*</td>
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Table 4. Brief Repeatable Battery Results

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<th>SRT CLTR</th>
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<th>SDMT</th>
<th>10/36 Correct</th>
<th>10/36 Delayed</th>
<th>WLG Task</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre</td>
<td>32.67 (9.93)</td>
<td>44.75 (11.89)</td>
<td>49.17 (18.22)</td>
<td>43.33 (20.96)</td>
<td>8.67 (2.64)</td>
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<tr>
<td>Post</td>
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<td>43.33 (11.20)</td>
<td>21.83 (5.97)</td>
<td>7.00 (2.56)</td>
<td>26.75 (9.63)</td>
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<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre</td>
<td>33.43 (12.67)</td>
<td>44.43 (19.52)</td>
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<tr>
<td>Post</td>
<td>34.14 (12.70)</td>
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<td>51.14 (4.43)</td>
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<td>8.58**</td>
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<td>0.01</td>
<td>0.26</td>
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Table 4. A display of BRB results for the omnibus ANOVA as well as each independent sub-component analysis. Mean values are presented for pre and post time points with standard deviation values in parentheses. The third row from the bottom illustrates a comparison of baseline level performance across groups. Statistically significant differences at T1 were controlled for in the final analyses. All BRB values were within 1.5 standard deviations of normative data provided by Boringa et al., 2001. The last row illustrates the results of Hotelling’s multivariate F-test and the obtained effect size in partial eta². †p-value<0.1, *p<0.05, **p<0.01. No results survived a Bonferroni correction at p<0.005.
Table 5. 9-Hole-Peg Test Results

<table>
<thead>
<tr>
<th>Group</th>
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<tr>
<td></td>
<td>Training</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
</tr>
<tr>
<td></td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>Control</td>
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<tr>
<td></td>
<td>Pre</td>
</tr>
<tr>
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<td>Post</td>
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<td>F-value</td>
</tr>
<tr>
<td></td>
<td>Partial eta²</td>
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</tbody>
</table>

Table 5. A display of results for the repeated measures ANOVA of dominant and non-dominant hand average 9-hole-peg performance in seconds. Mean values are presented for pre and post time points with standard deviation values in parentheses. The last row illustrates the results of the $F$-test and the obtained effect size in partial $\eta^2$. 


APPENDIX B:

Figures

Figure 1. Study Flow Chart

Figure 1 is a visual overview of the study specific details from recruitment to completion.
Figure 2 outlines how individuals were chosen for participation in the space fortress intervention based on inclusionary/exclusionary criteria, as well as attrition rates once individuals were randomized. An attrition rate of less than 22% provides substantial support for the feasibility of a hybrid-variable priority intervention.
Figure 3. A static image of the Space Fortress video game highlighted in the current proposal as a platform for testing the efficacy of the HVT approach in RRMS individuals.
Figure 4. A graphical representation of space fortress game analysis results. Time is displayed on the x-axis while game score values are displayed on the y-axis. Those data points in blue represent the training group and those in red represent the control group. **p-value<0.01, *p-value<0.05, †p-value<0.1. Alpha demarcation in the graph title represents F-test results, while those in the graph, itself, represent t-test results for each time point.
Figure 5. A graphical representation of the Brief Repeatable Battery transfer effect results. Time is displayed on the x-axis while raw test values are displayed on the y-axis. Those data points in blue represent the training group and those in red represent the control group.
Figure 6. 9-Hole-Peg Transfer Effect Results

Figure 6 is a graphical representation of results from the omnibus 9-Hole-Peg transfer effect results, as well as results for each individual hand. Time is displayed on the x-axis while seconds to complete are displayed on the y-axis. Blue data points represent the training group, and the control group appears in red.
Figure 7. Comparison of young adult participants and RRMS patients trained with 20 hours of HVT

Figure 7 is an illustration of game score differences after 20 hours of training in a group of twenty-five young adult participants as compared to a group of 12 RRMS participants. Data on young adults was adapted from Lee et al., 2011. The young adult sample is stratified by high scorers vs. low scorers to illustrate the difference in skill acquisition based on initial performance level. RRMS patients appear to score below the young adult sample at every time point.
APPENDIX C:
Self-report measures

HEALTH HISTORY QUESTIONNAIRE

Name: ________________________________

Date of Birth: ________________ (month/day/year)

Cardiovascular Disease Symptoms
Indicate the symptoms that you have experienced by circling or underlining Y (yes) or N (no).

1. Pain or discomfort in the chest, neck, jaw, arms or other areas that may be related to poor circulation Y N
2. Heartbeats or palpitations that feel more frequent or forceful than usual or feeling that your heart is beating very rapidly Y N
3. Unusual dizziness or fainting Y N
4. Shortness of breath while lying flat or a sudden difficulty in breathing which wakes you up while you are sleeping Y N
5. Ankle swelling unrelated to injury Y N
6. Shortness of breath at rest or with mild exertion (like walking two blocks?) Y N
7. Feeling lame or pain in your legs brought on by walking Y N
8. A known heart murmur Y N
9. Unusual fatigue with usual activities Y N

Recent Health Disturbances

10. Have you had any recent illnesses? Y N
    If you answered Yes for question 10, please explain.
11. Have you recently been hospitalized? Y N
   If you answered Yes for question 11, please explain.

12. Have you recently had any surgical procedures? Y N
   If you answered Yes for question 12, please explain.

13. Have you recently received antibiotics or a vaccination? Y N
   If you answered Yes for question 13, please explain.

14. Have you recently taken any anti-inflammatory drugs (besides aspirin)? Y N
   If you answered Yes for question 14, please explain.

15. Have you been diagnosed with any neurological disorder? Y N
   If you answered Yes for Question 15, please explain.
16. Have you been diagnosed with any psychiatric disorder?    Y    N

17. Have you been diagnosed with hypertension?    Y    N
   If you answered Yes for Question 17, please tell us what medications you are taking and if the hypertension is controlled.

18. Are you or could you currently be pregnant?
   Please list the date of your last menstrual cycle

MS diagnosis

19. What type of MS do you have?

20. When was your most recent exacerbation?

21. Are you currently taking corticosteroids?
   If no, have you taken corticosteroids in the past month?

Other Habits

22. How many cups of regular coffee do you have daily? ______
23. How many caffeinated soft drinks do you have daily? ______
24. How many cups of tea do you have daily? ______
25. How many cans of beer do you have weekly? ______
26. How many glasses of wine do you have weekly? ______
27. How many ounces of liquor do you have weekly? ______
28. How many cigarettes do you smoke daily? ______
29. How many cigars or pipes do you smoke daily? ______
30. If you are an ex-smoker, how many years since you quit? ______
31. How often would you rate your stress level as high?
   Occasionally    Frequently    Constantly
32. Do you wear dentures? ______
33. Do you wear glasses? ______
34. Do you wear contact lenses? ______
35. Do you take vitamins? Y N
   If you answered Yes for question 35, what type?
36. In your previous job, did you handle or breathe chemicals regularly? Y N
   If you answered Yes for question 36, please explain.
37. Please list anything else you feel we should know about you and your current/past health:
   (If you are female, have you had hormone replacement therapy):

BMI Prescreening
38. What is your height? (feet) (inches)
39. What is your weight (in pounds)?

Contact Information
40. Primary Physician:
   Name: ______________________ Phone number: ______________________
41. Hospital preference: _______________________

42. Emergency Contacts:
   Name: __________________ Phone number: __________________

   Name: __________________ Phone number: __________________

43. Allergies:

44. Chronic Conditions (Specifically, Sleep Apnea, severe arthritis, psoriasis, inflammatory disease, bowel disease, asthma, polyneuropathies, Lupus)

45. Please list the current medications that you take:
EDINBURGH HANDEDNESS INVENTORY

At any point in the past, have you ever written with your left hand? Y N

If yes, please explain:

For the following activities, please indicate which hand you use most often and what percentage of the time you use it.

<table>
<thead>
<tr>
<th>Activity</th>
<th>L</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holding a glass</td>
<td>___%</td>
<td>____%</td>
</tr>
<tr>
<td>Throwing a ball</td>
<td>___%</td>
<td>____%</td>
</tr>
<tr>
<td>Dealing cards (dealing hand)</td>
<td>___%</td>
<td>____%</td>
</tr>
<tr>
<td>Using an eraser</td>
<td>___%</td>
<td>____%</td>
</tr>
<tr>
<td>Entering numbers on a calculator</td>
<td>___%</td>
<td>____%</td>
</tr>
<tr>
<td>Using a spoon</td>
<td>___%</td>
<td>____%</td>
</tr>
<tr>
<td>Combing your hair</td>
<td>___%</td>
<td>____%</td>
</tr>
<tr>
<td>Brushing your teeth</td>
<td>___%</td>
<td>____%</td>
</tr>
</tbody>
</table>

For the following activities, please tell which hand you use the majority of the time, not whether you can use both hands.

If you were using a broom, which hand would be on top? L R

If you were hammering a nail, in which hand would you hold the hammer? L R

If you were washing dishes, in which hand would you hold the sponge? L R

If you were holding a bowl, which hand would you use to stir its contents? L R

If you were getting tape out of a dispenser, which hand would you use to pull the tape? L R

If you were threading a needle, in which hand would you hold the thread? L R

If you were tearing off the top of a package, which hand would you use to tear? L R

If you were holding a jar, which hand would you use to unscrew the lid? L R
APPENDIX D:
Screening scripts

PHONE SCRIPT

(The individual will contact the CNLab by phone and inquire about the study.) First, I would like to give you a little more information about what this study entails. This is a 12-week intervention study at the OSU campus for individuals with multiple sclerosis. Four of those weeks will be devoted to pre-intervention and post-intervention testing.

Two-weeks before the intervention begins, you will be asked to make a visit to the Clinical Neuroscience Laboratory. During this first visit, you will see a neurologist who will assess your disease severity and course. This assessment should take no longer than 1 hour. In this session, we will also introduce you to the training that you would participate in as part of the study group. This will involve watching a video and completing some practice tasks. This portion of the session should take no longer than 1.5 hours. If you have any problem with the study at any time and wish to withdraw, or if you do not complete screening, personal information collected from you will be shredded to ensure confidentiality.

At a second session, you will again be asked to visit the Clinical Neuroscience Laboratory. At this session you will be asked to fill out some questionnaires and take some computerized and paper and pencil tests to assess your thinking abilities. This entire session should take no longer than 3 hours to complete.

This entire process of tests will be completed after the intervention as well. At your completion of the pre-intervention testing, you will be randomized into either the active intervention group or a wait-listed control group. Randomization is much like flipping a coin. Your placement in either the control or active group will be completely by chance. The active group will then participate in a cognitive training intervention for 8 weeks. This will involve visiting the CNLab 2-3 times a week for 8 weeks. Throughout these 20 sessions, individuals will play video games designed to help your thinking process. After 8-weeks both the active intervention group as well as the wait-list control group will complete post-intervention testing. At this time, the wait-list control group individuals will be offered participation in the active intervention. Should they choose to accept, these individuals will then undergo the 8-week intervention.

Do you have any questions about this process? Are you interested in participating in this study? (If no, thank them for their time)

Your participation in this study is greatly appreciated and will help benefit research geared towards improving the lives of individuals with multiple sclerosis. We would also like you to know that participation in this interview is completely voluntary. You may cease participation at any time without penalty. Does that make sense?
If you have any more questions involving the study that you can’t think of right now, please don’t hesitate to contact us at 614-292-9568 or by email at ra@clinicalneurosciencelab.com.

So at this time, I would like to ask you some questions to see if you are a good candidate for this intervention. I would first like you to know that there is some risk of disclosure of your answers to these questions. However, in this lab, we are very meticulous with our subject materials. All you answers to these questions will kept on either an encrypted computerized database within this secure lab or as written documents within a locked file cabinet also kept within this lab. Your materials from this interview will be identifiable only by a number assigned to you. The key that ties your identification to this number will be kept on our computerized database. The entire laboratory is accessible only to individuals under supervision by Dr. Prakash. Your materials will be available only to key personnel on this study. If you choose not to participate in this study or are ineligible, the materials collected from this phone interview will be discarded to ensure confidentiality. However, if you would like to be contacted for future studies, we will keep this material on file to expedite your next screening process. Would you like to be contacted for future studies? Is it all right with you that we keep this information on file? Would you still like to proceed with the rest of the interview?

Thank you. Now I will ask you some basic questions about your demographics and health history.(collection of basic contact information)

1. What is your birth date? (computerized database will calculate age from this).
2. Do you have any history of neurological disorders other than MS? Examples would include Alzheimer’s, traumatic brain injury or something similar.
3. Do you have any history of psychiatric disorders? Examples would include anxiety, depression, schizophrenia or something similar.
4. Are you currently taking any medication? Could you tell me what those medications are?
5. What was the date of your last exacerbation?

Thank you for answering all of those. Now I would like to ask you a little bit about your previous experience with video games. This could affect how you perform on the intervention. Is that all right? Great

1. How many times in the past year have you:
   a. Played a PC based video game?
   b. Played a console video game system? (like Wii or Playstation)
   c. Played a video game in a an arcade?
   d. Played an online java-script video game? (www.addictinggames.com for example)
2. Do you consider yourself to be an active video game player?
3. During an average week, how many hours will you spend playing video games?
4. How often did you play video games as a child?
5. Do you own a personal computer?
6. Please list for me any video game systems you have in your household.
7. Please estimate the number of hours per week that you:
   a. Play PC based video games
   b. Play console video games
   c. Play video games in an arcade
   d. Play online java-script games

Thank you so much for answering all of those. (At this time we would let the individual know their eligibility for the study and schedule their first session.)
Control Group Phone Call Checklist

1. Has the individual suffered an exacerbation within the past two weeks?

2. Has the individual taken corticosteroids within the past two weeks?

3. Is there any chance the participant could be pregnant?

4. Are there any new medications the participant is taking?

5. Has the participant experienced any severe stressors within the past two weeks?

6. Is the participant currently participating in any other studies at this time?

7. Have there been any significant changes in the participant’s lifestyle (diet, exercise, sleep habits)?

8. Are there any additional concerns the participant would like to bring to our attention?