Rehabilitation of Executive Dysfunction in Multiple Sclerosis: Cognitive, Behavioural and Neurophysiological Effects of Goal Management Training

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Department of Psychology
University of Toronto

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Abstract

Multiple sclerosis (MS) is a chronic, progressive central nervous system disease characterized by distributed white matter injury. Particularly prevalent in Canada, MS is a leading cause of disability with extended personal and societal costs given its early onset (on average between 20-40 years of age). Deficits in executive functioning are common and detrimental to employment, daily functioning and quality of life, however their precise nature remains underspecified. Two studies were undertaken to: (1) describe the executive processes affected in MS, including neurophysiological correlates, and (2) explore, in a double-blind randomized controlled trial, patients’ response to an intervention for improving behavioural self-regulation. Study 1 described significant functional limitations and impairments in processing speed and executive control of attention, memory and working memory in MS patients, both relative to neurologically healthy controls and as a monotonic function of disease severity. Mean amplitudes for event-related potentials (ERPs) including the P3 and the error-related negativity and positivity (ERN, Pe) were linked to behavioural markers of attention control and performance monitoring. ERP amplitudes and ERP-behavioural associations appeared sensitive to the presence and severity of executive dysfunction related to disease progression. In Study 2, these impaired MS patients
were randomly assigned to a modified version of Goal Management Training (GMT) or a psycho-educational control group (Brain Health Workshop, BHW). In GMT, patients learned stepwise strategies ("Stop-State-Split") to keep "on track" in their daily activities, including mindfulness training to enhance attentional awareness and control. Rehabilitation outcomes were assessed post-training and at a 6-month follow-up using a multi-level battery. Compared to BHW, GMT was associated with greater improvement on tests of executive-attentional processes as well as functional task performance and observable functioning in daily life activities. ERP-behavioural changes provided corollary evidence of improved self-regulatory processing. This study is among the first to demonstrate improvement in executive functioning compared to an active control condition in MS patients with a range of disease severity and with effects remaining visible at six months. While replication in a larger sample size is needed, results suggest GMT as a potentially effective approach for executive and self-regulatory impairment in people with MS.
Acknowledgments

So many people contributed to this endeavor – either directly or, just as importantly, in keeping me passably sane all these years – that it will be impossible to thank them all. The obvious place to start is with Brian Levine… for showing me how to navigate in a field at once full of promise and pitfalls. I hope to keep that bar up where you set it. I also thank Randy McIntosh for helping me keep my stats up to snuff, and Gus Craik for the wisdom of his experience. I humbly appreciate the value of having had such a triumvirate for my supervisory committee.

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I dedicate this work to my mum. We both wished you could have lived to see me cross this finish line, though you left me with your faith I would get here eventually. I literally couldn’t have done it without you and Dad. Your unwavering persistence all those years ago in finding a school that would “take” me… with Dad’s commitment to carrying me, every day until they made it wheelchair-accessible, up and down the stairs of that little primary school… that was really where this whole road started. I am eternally grateful and proud to have been your daughter.
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<tr>
<td>ADHD</td>
<td>Attention-deficit hyperactivity disorder</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>BHW</td>
<td>Brain Health Workshop</td>
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<td>BSR</td>
<td>Bootstrap ratio</td>
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<td>CFQ</td>
<td>Cognitive Failures Questionnaire</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>cvRT</td>
<td>Coefficient of variation of reaction time</td>
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<td>DEX</td>
<td>Dysexecutive Questionnaire</td>
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<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<tr>
<td>DS</td>
<td>Digit span</td>
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<tr>
<td>DWMI</td>
<td>Diffuse white matter injury</td>
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<tr>
<td>EDSS</td>
<td>Expanded Disability Severity Scale</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>ERN</td>
<td>Error-related negativity</td>
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<td>ERP</td>
<td>Event-related potential</td>
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<tr>
<td>FAS</td>
<td>Phonemic fluency to letter cues F, A and S</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>GAS</td>
<td>Goal Attainment Scaling</td>
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<td>GMT</td>
<td>Goal Management Training</td>
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<tr>
<td>JLO</td>
<td>Judgment of Line Orientation</td>
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<td>LV</td>
<td>Latent variable</td>
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<td>MBSR</td>
<td>Mindfulness-based stress reduction</td>
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<td>MEG</td>
<td>Magnetoencephalography</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>MET</td>
<td>Multiple Errands Test</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>mPFC</td>
<td>Medial prefrontal cortex</td>
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<tr>
<td>μV</td>
<td>Microvolts</td>
</tr>
<tr>
<td>NAWM</td>
<td>Normal-appearing white matter</td>
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<tr>
<td>PASAT</td>
<td>Paced Auditory Serial Addition Test</td>
</tr>
<tr>
<td>Pe</td>
<td>Error-related positivity</td>
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<tr>
<td>PES</td>
<td>Post-error slowing of reaction time</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
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<tr>
<td>PLS</td>
<td>Partial Least Squares</td>
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<tr>
<td>POMS</td>
<td>Profile of Mood States</td>
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<td>PPMS</td>
<td>Primary-progressive multiple sclerosis</td>
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<tr>
<td>PSQI</td>
<td>Sleep Quality Index</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>RRMS</td>
<td>Relapsing-remitting multiple sclerosis</td>
</tr>
<tr>
<td>RT</td>
<td>Reaction time</td>
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<tr>
<td>SART</td>
<td>Sustained Attention to Response Task</td>
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<tr>
<td>SDMT</td>
<td>Symbol Digit Modalities Test</td>
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<tr>
<td>SPMS</td>
<td>Secondary-progressive multiple sclerosis</td>
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<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
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<tr>
<td>TEA</td>
<td>Test of Everyday Attention</td>
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<tr>
<td>WCST</td>
<td>Wisconsin Card Sorting Test</td>
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Chapter 1
Introduction

The executive functions comprise the highest level of human cognitive abilities and are essential for self-regulation. Supported by distributed neural networks, they are among the cognitive functions most vulnerable to distributed brain injury, such as occurs in multiple sclerosis (MS). Modern medical treatment of MS may delay the onset of cognitive deficits but there are as yet no standard interventions to improve functioning in MS patients with executive impairment. This project explored the feasibility and utility of a theory-based cognitive rehabilitation protocol for executive dysfunction in MS patients at varying stages of disease progression.

This introductory chapter provides an overview of the cognitive processes subsumed in theories of executive functioning, their relation to brain structure and function and a brief review of select behavioural and neuroimaging methods for their assessment. This will include a brief discussion of recent research on mindfulness and its relevance to neurocognitive mechanisms supporting self-regulation. It will be shown that executive dysfunction can arise from conditions producing focal and/or distributed brain damage including multiple sclerosis. A review of cognitive rehabilitation research, with an emphasis on approaches for executive and self-regulatory deficits, will highlight limitations in the quantity and quality of available protocols, particularly for individuals with MS. The evolution of Goal Management Training (GMT) as a theory-based approach for self-regulatory impairment will be described together with a review of evidence for its effectiveness in focal- and distributed-injury patient groups.

From this background, the rationale and specific hypotheses for this dissertation are described in Chapter 2, with methods detailed in Chapter 3. Two studies were completed, to (1) evaluate neurocognitive aspects of executive dysfunction as these relate to MS disease progression and (2) validate GMT as an intervention for executive deficits in this population; results are described in Chapters 4 and 5, respectively. Discussion of these results and conclusions are presented in the sixth and final chapter.
1.1 Executive control, goal-directed behaviour and supervisory attention

The “executive functions” are a collection of related cognitive processes that allow formulation and execution of goals, including monitoring and adjusting behaviour as needed to support goal attainment. To paraphrase Lezak and colleagues (1982; 2004), key components of the executive functions (EF) include: (1) volition and capacity to formulate a goal or intention; (2) planning what steps and/or resources are required to achieve that goal; (3) translating the plan into purposeful action, typically involving complex sequencing and coordination of behaviour; resulting in (4) behaviour that is self-regulated (monitored and corrected) as needed to be effective in reaching the goal. Each of these components requires a number of processes. Volition, for example, depends on awareness of one’s present state, including social and situational context, and one’s capacity to envision future states (thus potential goals) as well as the motivation to move toward them. Together, the executive functions are necessary for self-management and for flexible, adaptive and independent daily functioning in a manner that is situationally and socially appropriate. They are what allow us to “transcend the default mode” of stimulus- or impulse-driven behaviour, by enabling neuronal – and ultimately behavioural – responses that are “contingent” (ergo flexible and adaptable) rather than purely reactionary (Mesulam, 2002). Understanding and description of the specific nature of both affective and cognitive aspects of self-regulatory control continue to evolve, as do neurocognitive models of their relation to brain structure and function.

Historically, such self-regulatory processes were first defined clinically, from behavioural anomalies shown by patients with frontal lobe damage (Damasio, Anderson, & Tranel, 2012; Harlow, 1868; Luria, 1966; Shallice & Burgess, 1991). For this reason, the terms “executive functions” and “frontal [lobe] functions” have been used interchangeably (e.g., Stuss & Knight, 2002). A common theme running through such clinical reports was the observation that patients with frontal lobe damage (the extent of which was difficult to delineate prior to modern neuroimaging) typically retained normal-range functioning in “basic” neurological domains (perception, sensation, language abilities, motor functions, core aspect of memory, and so on) – to the extent they might appear to have “recovered” (Bigelow, 1850; Hebb, 1942) – yet were unable to function in a purposeful, effective way in the “real world” of their daily lives. Some, most often with damage to ventro-medial prefrontal cortex and/or associated subcortical or
3

limbic areas causing affective or motivational disturbance, get “stuck” at the volition stage and will not independently initiate goal-oriented behaviour (Levy & Dubois, 2006; Marin & Wilkosz, 2005) or will make but then rapidly abandon goals (Mesulam, 2002). Others, particularly with damage to dorsolateral prefrontal cortex and/or associative substrates causing a more “cognitive” disturbance, have been characterized as running into difficulty generating a useful, effective plan of action, particularly in lesser-defined (i.e., more ambiguous) contexts (Goel & Grafman, 2000; Levy & Dubois, 2006; Zalla, Plassiart, Pillon, Grafman, & Sirigu, 2001).

Even with an intention or plan, difficulty translating these into effective, goal-directed action is a hallmark of executive dysfunction. Goal-directed action requires engaging, maintaining, stopping and switching between behavioural sequences (Lezak, et al., 2004) in a flexible manner that can adapt to internal and external feedback and to unplanned events. Whereas well-learned, routine complex action sequences may be managed by such patients (Shallice & Burgess, 1991), situations that are novel, ambiguous, fluid and/or present opportunities for distraction are challenging. Patients’ deficits in monitoring or “supervising” their actions with respect to their intentions can lead to inefficient action sequences or the insertion of goal-irrelevant actions (Norman & Shallice, 1986). In such “action lapses” or “capture errors” (Shallice, 1982) a task-irrelevant thought or environmental input triggers an action sequence that derails the goal-directed action plan.

Building on existing views of this centrality of goals to purposeful action (Lezak, 1982; Luria, 1966; Shallice, 1982), Duncan (1986) described healthy “organized” (i.e., executive) behaviour as an iterative process in which goals (and subgoals) are constructed to resolve demands (either internal or environmental), then consulted to select action sequences that will move one from the “current” state to the “goal” state. Depending on the success of each action (which would be harder to predict in a novel, ambiguous or fluid situation), new actions may need to be planned and implemented – hence the requirement to continually consult (i.e., mentally re-activate) one’s goal. (It may also be the case that the goal itself needs to be altered if proven unattainable despite an organized program of action.) A critical point is that the individual must independently construct and consult the goal list. When explicitly questioned, dysexecutive patients are often able to state a goal – the deficit lies in using the goal to direct behaviour. It is in this dissociation of intact knowledge from use of this knowledge to guide behaviour that patients show “goal neglect” (Duncan, Emslie, Williams, Johnson, & Freer, 1996).
The cognitive processes and neural substrates supporting executive control and goal-directed behaviour continue to be actively studied. From earlier concepts of a “general” or “central executive” (Baddeley & Hitch, 1974; Shiffrin & Schneider, 1977) and related unitary views of the representational nature of prefrontal cortex (Goldman-Rakic, 1987), there has been some progress in fractionating component executive processes, with parallel interest in identifying functional subregions of prefrontal cortex. In addition to the dorsal/ventral affective/cognitive regional distinction (Levy & Dubois, 2006; Stuss & Levine, 2002), further divisions have been drawn between cognitive processes. Examples include the distinctions between maintaining and manipulating information held in working memory (D’Esposito, Postle, Ballard, & Lease, 1999), or between shifting (response sets), updating (the content of mental representations) and inhibiting (prepotent responses) (Miyake, et al., 2000).

Attention – the selection of which information from within the continual stream of internal and external input enters awareness and is subjected to higher processing (Broadbent, 1958; Handy, Hopfinger, & Mangun, 2001; James, 1890) – is also now viewed as a multi-faceted cognitive domain. Attention may be engaged through either bottom-up (stimulus-driven, automatic) or top-down (goal-directed, controlled) means (Buschman & Miller, 2007; Desimone & Duncan, 1995). Posner and Petersen’s (1990) influential review described three main attentional systems: (1) a posterior brain system that carries out involuntary, stimulus-driven attentional orienting; (2) an anterior system that mediates voluntary (goal-directed) selective attention; and (3) an alerting or vigilance system that enables one to prepare and sustain a state of readiness to detect and respond to task-relevant stimuli. Rather than being entirely separate from the posterior system, the anterior system extends it by adding the element of executive control to allow for goal-driven allocation of attentional resources. Similar in concept to the “supervisory attention system” described by Norman and Shallice (1986), this view of executive control of attention has since been modeled as itself having multiple component processes: energizing or inhibiting schemata (i.e., action plans or scripts), setting criteria for their implementation and monitoring / adjusting behaviour to optimize task performance (Stuss & Alexander, 2007; Stuss, Shallice, Alexander, & Picton, 1995). Conceptual overlap with broader models of executive functioning (Miyake, et al., 2000) highlights the central role of attention in executive control (Kane & Engle, 2002; Shallice & Burgess, 1991; Shiffrin & Schneider, 1977).
As discussed in a later section, models of executive and attentional control have been informed by and mapped onto structural brain divisions through a combination of neuroimaging studies and neuropsychological studies of patients with lesions and corresponding cognitive-behavioural impairments. Increasingly, however, neuroscience is also (re)emphasizing the need to understand the functional integration of such “nodes” into larger scale neural networks that support dynamic, multi-level information processing and adaptive goal-directed behaviour (Bressler & Menon, 2010; McIntosh, 2000; Mesulam, 1990; Miller & Cohen, 2001).

1.1.1 Functional significance of executive processes

As the last group of cognitive abilities to mature during human development (Blakemore & Choudhury, 2006; Luna, Garver, Urban, Lazar, & Sweeney, 2004), the executive functions are central to adult levels of functional independence, productivity, self-management and social relations. Executive impairment can have a significant impact on real-life functioning, causing marked disability. By definition, executive dysfunction limits the self-awareness and problem-solving that patients would need to independently recognize and adapt to or work around the impairment, leading to a greater functional burden than typically accompanies lower-level disabilities such as physical or sensory impairments. In patient populations that may be affected by both physical and cognitive limitations, for example multiple sclerosis (MS), executive deficits typically limit employment, social activities and household responsibilities beyond the limitations of physical disabilities alone (Bobholz & Rao, 2003; Rao, Leo, Ellington, et al., 1991; Ron & Feinstein, 1992). In addition to the resulting costs to patients, their families and the larger economy (Canadian Institute for Health Information, 2007; Multiple Sclerosis International Federation, 2010; Ponsford & Schönberger, 2010) executive deficits and the associated loss of functioning are associated with poorer quality of life (Levine, Dawson, Boutet, Schwartz, & Stuss, 2000; Macciocchi, Reid, & Barth, 1993; Mitchell, Kemp, Benito-León, & Reuber, 2010; Rosti-Otajärvi & Hämäläinen, 2011) including potential development of depression and anxiety disorders (Rao, Leo, Ellington, et al., 1991; Whelan-Goodinson, Ponsford, Schönberger, & Johnston, 2010).

1.1.2 Neuropsychological assessment

Executive functioning is one of the most difficult cognitive domains to assess in a laboratory or clinical setting, given the challenge inherent in the “paradoxical need to structure a situation in
which patients can show whether and how well they can make structure for themselves” (Lezak et al., 2004, p. 611). The past several decades have seen a growing number of assessment procedures, though some of these were later shown to have rather poor sensitivity and/or specificity to executive deficits (Levine, Katz, Dade, & Black, 2002; Lezak, 1982). While still clinically useful, popular tests such as the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993) and Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) depend on a number of interacting component processes (Monchi, Petrides, Petre, Worsley, & Dagher, 2001). Further, such “executive” or “frontal” tests generally reflect only the more “cognitive” facets of self-regulation (Stuss & Levine, 2002). In clinical practice, assessment of social, volitional and affective dysregulation still relies heavily on clinician observation, patient history and caregiver reports. It must also be recognized that available tests are imperfect at capturing even the cognitive facets of executive dysfunction, particularly when subtle, and clinical as well as caregiver observations of how patients approach tasks are as essential as metrics of tasks performance.

As knowledge is translated from neuroscience to clinical practice, tests have also become increasingly fractionated by process. In some cases, multiple such tests are grouped into batteries meant to cover (and provide subscores for) multiple facets of executive functioning (e.g., Delis, Kaplan, & Kramer, 2001; Wilson, Alderman, Burgess, Emslie, & Evans, 1996). Several tests are also commonly used to measure controlled (i.e., executive or supervisory) aspects of attention, and some of these also grouped into batteries. The Test of Everyday Attention (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996b), for example, includes subtests differentially weighted in their requirement for sustained/vigilant attention, selective/focused attention and attentional switching (between stimulus-response sets) as demonstrated through factor analysis in both neurologically healthy and dysexecutive patient samples (Chan & Lai, 2006; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996a).

Assessment may also benefit from inclusion of tasks used in or adapted from experimental cognitive research (Levine, et al., 2002; Stuss & Levine, 2002). Defined as the endogenous (goal-directed) maintenance of attention over an extended period of time, e.g. to track or respond to “target” events based on task instructions (Posner & Peterson, 1990; Robertson & Garavan, 2004), sustained attention (vigilance) was first investigated with “watch-keeping” tasks. These involve detecting and responding to rarely and unpredictably occurring target events against an
unchanging and/or task-irrelevant background (Cohen, et al., 1988; Pardo, Fox, & Raichle, 1991; Paus, et al., 1997; Whyte, Polansky, Fleming, Coslett, & Cavallucci, 1995). However, in this context the target events may become salient enough to trigger bottom-up attentional engagement. With all non-target events requiring no response, the goal-based stimulus-response schema faces little competition; supervisory attention is not required. Thus, vigilance tasks requiring sustained “performance” may not require sustained control of attention.

The Sustained Attention to Response Task (SART; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) inverts the traditional vigilance paradigm. Single digits (1 through 9) are randomly and rapidly presented with the subject pressing a response key to all digits except the number ‘3’. The rare and unpredictable occurrence of these “no-go” trials (11% of all trials) creates a demand for sustained attention and goal awareness throughout the test. The task goal (inhibit responding to the number ‘3’) must be continually reactivated in the face of competition from the prepotent stimulus-response schema that is set up by participants’ continual rapid response to the stream of “go” digits (Manly, Robertson, Galloway, & Hawkins, 1999; Robertson, et al., 1997).

Attentional and action “lapses” during this task result in commission errors (failing to withhold a response to ‘3’ on the no-go trials) and, less frequently, omission errors (failing to respond on go trials). The near-continual stream of respose time data across go trials also permits tracking of transient fluctuations in attentional control linked to goal neglect and reactivation (Smallwood, et al., 2004), as within-subject reaction time speeding associates with automatic, non-attentive responding (Parasuraman, Warm, & See, 1998). Conversely, neurologically healthy participants show slower reaction times following commission errors (“post-error slowing”) indicative of performance monitoring and the upregulation of executive control (Dutilh, et al., 2012). This behavioural correction is less reliably observed in dysexecutive patients following brain injury (Manly, et al., 1999; Robertson, et al., 1997).

While the fractionated, construct-driven approach has proven useful both experimentally and clinically, there has also been interest in developing more “ecologically valid” tests that may better approximate the real-life, complex and multi-process situations in which executive dysfunction may be most apparent (Burgess, et al., 2006; Wilson, 2008). Well-validated examples include the Multiple Errands Test (Shallice & Burgess, 1991) and Hotel Test (Manly, Hawkins, Evans, Woldt, & Robertson, 2002). In giving patients a “to-do” list of errands to be carried out in an actual shopping concourse, the MET may be the most representative available
paradigm to capture the contingencies and loose structure that characterize real-life situations that demand executive functioning (Goel & Grafman, 2000; Lezak, et al., 2004). Further, its use has advanced conceptual understanding of executive dysfunction (Dawson, et al., 2009; Shallice & Burgess, 1991). However, the need to develop location-specific protocols, training on scoring procedures and lengthy administration time that accompany the MET’s grounding in a real-world context also limit its practicality as an assessment tool.

Adapted from the influential Six Elements Test (Shallice & Burgess, 1991), the Hotel Test is easier than the MET to implement in an office or research setting while retaining materials and setting up a task situation that is representative of a realistic multi-tasking work environment. Patients are asked to imagine they are running a hotel, and to attempt some of each of five clerical tasks (compiling bills, sorting money, looking up phone numbers, sorting name tags and proof reading a pamphlet) with an additional prospective memory task (remembering to press the buttons to open and close a “garage door” for “deliveries” at pre-specified times). As completion of each of the clerical tasks would far exceed the 15 minutes patients are given, the Hotel Test requires patients to maintain the overarching goal to sample each of the five tasks while resisting the stimulus-driven impulse to complete any one task. Doing so requires performance monitoring and switching attention between tasks. As in earlier versions of the Six Elements Test (Shallice & Burgess, 1991; Wilson, et al., 1996), dysexecutive patients have been shown to get caught up in the component Hotel tasks and neglect the overall goal of attempting all tasks, despite intact knowledge of the goal on questioning – demonstrating the classic dissociation of intention and action (Duncan, 1986).

While such tests have enabled better quantification of dysexecutive behaviour (Levine, et al., 2002), qualitative self- and caregiver-reports remain important in describing executive or self-regulatory deficits apparent in the patient’s daily life activities. Patients’ endorsement of items on the Cognitive Failures Questionnaire (CFQ; Broadbent, Cooper, Fitzgerald, & Parkes, 1982) provides an index of everyday cognitive deficits that indicate a tendency to absent-mindedness and action slips (Robertson, et al., 1997; Shallice, 1982). Factor analysis of items on the Dysexecutive Questionnaire (DEX; Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Wilson, et al., 1996) has shown the DEX to be sensitive to everyday failures of inhibition, intentionality and executive aspects of memory as well as emotional lability (“positive affect”) and emotional blunting or apathy (“negative affect”). Both patient and observer (“other” or “informant”) forms
are available for the DEX, which confers the benefit of probing patient insight. Poor insight is suggested when patients report significantly fewer deficits than are observed by their caregivers (e.g., Schweizer, et al., 2008), a pattern not seen in neurologically healthy controls (Burgess, et al., 1998). Various other rating scales are also available to assess the impact of patients’ cognitive and psychosocial functioning on participation in vocational or leisure activities, including the Head Injury Family Interview (Kay, Cavallo, Ezrachi, & Vavagiakis, 1995), Disability Rating Scale (Hall, Cope, & Rappaport, 1985; Rappaport, Hall, Hopkins, Belleza, & Cope, 1982) and Sickness Impact Profile (Bergner, Bobbitt, Carter, & Gilson, 1981; Levine, Dawson, et al., 2000). Goal Attainment Scaling (GAS; Kiresuk & Sherman, 1968; Kiresuk, Smith, & Cardillo, 1994) has been used for several decades as a means for patients to identify meaningful and specific treatment goals in various rehabilitation settings and has been well-validated to quantify treatment outcomes (Hurn, Kneebone, & Cropley, 2006) in terms of change relative to pre-treatment performance in the identified goal area. As such, GAS may be an underused but valuable tool for assessing goal neglect in dysexecutive patients.

In addition to clinical utility, self- and informant-report measures have also been useful in the clinical and ecological validation of the more construct-driven or process-oriented tests. For example, SART commission (no-go) errors are more frequently made not only by patients with mild through severe traumatic brain injury (TBI) in comparison to controls, but also by neurologically healthy controls who report a greater tendency for absentmindedness in daily life on the CFQ (Dockree, et al., 2004; Garavan, Ross, Murphy, Roche, & Stein, 2002; Manly, et al., 1999; Robertson, et al., 1997).

1.1.3 Neural correlates

1.1.3.1 “Nodes” within “networks”

As noted above, neuropsychological study of patients with brain injuries has significantly driven progress in understanding and description of the executive functions including attentional control. Within the past several decades, neuroimaging of both healthy and injured brains have added enormously to this literature. Both driven by and contributing to the “process” orientation in characterizing executive functioning, these bodies of research have enabled increasingly specific descriptions of brain-behaviour relations. This has included delineation of structural divisions within prefrontal cortex (PFC; e.g., Petrides & Pandya, 1994; Stuss & Levine, 2002), as
well as their associated cortical and subcortical pathways (Alexander, DeLong, & Strick, 1986; Petrides & Pandya, 2002).

Examining regional activity associated with specific task demands has also revealed functional dissociations within PFC. For example, monitoring task demands and allocating attentional resources have been associated with medial prefrontal (mPFC) and anterior cingulate cortex (ACC), while lateral PFC appears to be more instrumental in maintaining task “set”, representing task-relevant and suppressing interfering information (Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; King, Korb, von Cramon, & Ullsperger, 2010; MacDonald, Cohen, Stenger, & Carter, 2000; Van Veen & Carter, 2002a). Consistent with these results and the brain-behaviour relations they posited in their model of component supervisory (anterior) attentional functions (Stuss, et al., 1995), Stuss and colleagues observed regional dissociations between superior mPFC / ACC (initiating and maintaining readiness to respond), left dorsolateral (DL) PFC (setting response schema) and right DLPFC (monitoring performance, maintaining relevant response schema and suppressing irrelevant representations) (Stuss & Alexander, 2007; Stuss, Binns, Murphy, & Alexander, 2002).

Further executive-attention functional specializations have been described in subcortical and non-frontal cortical regions, particularly the thalamus and parietal cortex (Behrmann, Geng, & Shomstein, 2004; Bisley & Goldberg, 2010; Kanai, Dong, Bahrami, & Rees, 2011; Posner & Peterson, 1990; Van der Werf, et al., 2003). Overall, the locationist or modular approach of lesion studies and most neuroimaging research has amassed significant insight into many component cognitive processes. In some domains, function and structure have appeared to coincide quite neatly, e.g. in the primary motor and sensory cortices.

However, the higher-level executive and attentional functions are not as readily mapped to discrete areas but instead seem to involve multiple nodes working together to integrate information from and exert control over more basic levels of information processing, such as visual perception. For example, executive control of attention, driven by lateral prefrontal regions (though interaction with ACC), has been shown to modulate activity in primary and visual association cortices (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991; King, et al., 2010; Pessoa, Kastner, & Ungerleider, 2003). Models of functional and effective connectivity show parietal and thalamic attention-related regions as intermediaries in this top-down
executive-attentional biasing of stimulus processing (Buchel & Friston, 1997; Greenberg, et al., 2012; Lauritzen, D'Esposito, Heeger, & Silver, 2009; Mottaghy, et al., 2006; Saalmann, Pinsk, Wang, Li, & Kastner, 2012). The earliest of these studies may in fact have stimulated some of the first models of brain function as dynamic cross-regional interactions – in this case, functionally integrating the “sources” and “sites” of attention (Coull, 1998).

Thus, executive and attentional networks integrate the functional contributions of their nodes. For example, interactions of ACC and DLPFC enhance cognitive control through monitoring performance and signaling a need for behavioural adjustment (MacDonald, et al., 2000; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Silton, et al., 2010). Accordingly, ACC activation associates with attentional demands between trials within tasks (Silton, et al., 2010) as well as between tasks with different demands for attention, e.g. with greater involvement in divided attention compared to simple selective attention conditions (Corbetta, et al., 1991). The ACC-DLPFC interaction has also been attributed to the link between sustained attention and arousal (Robertson & Garavan, 2004; Sturm, et al., 1999), which is not dissimilar to the notion of sustaining “readiness” to exert the appropriate behaviour throughout tasks that present competing response schemas (Menon, Adleman, White, Glover, & Reiss, 2001; Stuss, et al., 2002)¹. Sustained attention tasks including the SART (Robertson, et al., 1997) have been consistently associated with a frontal-thalamic-parietal network, particularly in the right hemisphere (Garavan, et al., 2002; Mottaghy, et al., 2006; O’Connor, Robertson, & Levine, 2011; Pardo, et al., 1991; Posner & Peterson, 1990; Sturm, et al., 1999) that may further include ACC to maintain and enhance cognitive control as seen in participants with inherent or injury-related weakness in endogenously sustaining attention (Garavan, et al., 2002; Richard, O’Connor, Robertson, & Levine, 2010; Righi, Mecacci, & Viggiano, 2009).

Maturation of neural connections and the resulting development of such integrative neural networks are seen into adolescence, paralleling the emergence of adult-level executive functioning capacity (Blakemore & Choudhury, 2006; Hwang, Velanova, & Luna, 2010; Supekar & Menon, 2012). At the other end of the developmental spectrum, age-related declines

¹ Noting, however, that arousal is also a component of involuntary, salience-driven attentional capture through ascending neural pathways (Aston-Jones, Rajkowksi, Kubiak, Valentino, & Shipley, 1996; Lesica, et al., 2006)
in executive control accompany reduced functional connectivity in the associated networks (Campbell, Grady, Ng, & Hasher, 2012; Charlton, et al., 2006; Fjell, Westlye, Amlien, & Walhovd, 2011). In the healthy adult brain, neural networks established through maturation and experiential learning provide the anatomical basis for a balance between functional segregation and integration, allowing for rapid generation and transfer of information (Mesulam, 1990; Sporns, Chialvo, Kaiser, & Hilgetag, 2004). Neural networks thereby provide a means of extending the range of processing states that could be achieved though their component nodes acting in isolation, with concomitant increase in behavioural flexibility and accuracy (Bressler & Menon, 2010; McIntosh, 2000; Mesulam, 1990).

Such behavioural adaptiveness is a hallmark of executive functioning. From the foundation laid by research focused on functional localization, more recent research from a network viewpoint confirms that regions of lateral prefrontal and parietal cortices, cingulate cortex and subcortical structures including the thalamus form the key nodes of an executive-attention control network that supports goal-directed behaviour across specific task or stimulus boundaries (Knight RT, 1999; Miller & Cohen, 2001). This modern neurocognitive view of executive processes is not entirely new but rather an evolution from earlier views of brain organization. For example, in his conceptualization of primary, secondary and tertiary cortical zones, Luria (1966) had already highlighted the integrative nature of the executive functions. The intervening decades of research have refined knowledge of the anatomical bases for the balance between specialization and integration that characterize brain functioning.

The importance of the frontal lobes to executive functioning, that was apparent in the earliest clinical case studies (Harlow, 1868), may now be understood in the context of anatomical, functional and effective connectivity. As the most heavily connected “hub” in a network supporting executive and attentional control, prefrontal cortex – particularly DLPFC – is the likely driving force of network engagement (Mesulam, 1990). Coactivation of dorsal anterior cingulate cortex and medial prefrontal regions is common (Duncan & Owen, 2000) and may support participant engagement, which some have described as arousal (Mottaghy, et al., 2006), personal salience (Seeley, et al., 2007), and/or effort in monitoring performance and regulating cognitive control (Garavan, et al., 2002; MacDonald, et al., 2000; Richard, et al., 2010; Ridderinkhof, et al., 2004; Righi, et al., 2009; Silton, et al., 2010).
1.1.3.2 Neurophysiological correlates: Event-related potentials

With its discovery nearly a century ago, scalp-recorded electroencephalography (EEG) is the oldest method of measuring neural activity (Berger, 1929; Luck, 2005). The first event-related potentials (ERPs) to be averaged from continuous EEG measured sensory processing (Davis, Davis, Loomis, Harvey, & Hobart, 1939). Components associated with cognitive processes such as response readiness (Stuss, et al., 1995; Walter, Cooper, Aldridge, McCallum, & Winter, 1964) and top-down influences on sensory components emerged in ensuing decades.

The executive control of attention that has been shown – using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) – to modulate interregional connectivity and thereby enhance stimulus processing (Buchel & Friston, 1997; Lauritzen, et al., 2009) is also presumed to underlie attention-related modulation of sensory and cognitive stimulus-induced ERPs (Coull, 1998). Of these, the most studied cognitive component is the P3 or P300 (Luck, 2005), which was first identified in a comparison of expected and unpredictably appearing stimuli (Sutton, Braren, Zublin, & John, 1965).

The P3 is a positive deflection peaking within an approximately 250-500 millisecond (ms) post-stimulus-onset interval. When comparing the voltage amplitude of the P3 elicited by stimuli within various task contexts (Polich, 2007), it has been consistently found that P3 amplitudes are greater for stimuli that are novel or rare (Courchesne, Hillyard, & Galambos, 1975; Duncan-Johnson & Donchin, 1977) and for stimuli processed with greater attention, e.g. in spatially attended locations (Eimer, 2000; Heinze, Luck, Mangun, & Hillyard, 1990) or in focused (compared to divided) attention conditions (Isreal, Chesney, Wickens, & Donchin, 1980; Kramer & Strayer, 1988). “Novelty” effects on the P3 tend to have a more frontal topography, whereas “attention” effects tend to be more prominent over parietal sites (Bledowski, et al., 2004) though are also visible at frontal sites (Soltani & Knight, 2000). These effects are respectively labeled as P3a and P3b subcomponents in some studies (Katayama & Polich, 1998; Polich, 2007) though in contexts that may elicit both they are not distinguishable without experimental manipulation. Both have been related to attentional processes; these appear to be more stimulus-driven for the

\[ \text{Hence the original P300 label; between-study variability in peak latency had led many to instead use the label P3 as it follows the sensory P1 and P2 components.} \]
P3a and goal-driven for the P3b (Chennu & Bekinschtein, 2012). As would be expected for components that reflect neural activity in attentional networks, the topography of both the P3a and P3b are believed to reflect summation from multiple sources including frontal, parietal and cingulate cortices (Linden, 2005; Soltani & Knight, 2000). Topographical changes have been reported in participants with poorer executive functioning due to aging or brain disease associated with altered network functioning (Adrover-Roig & Barceló, 2010; Linden, 2005; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Hutchinson, et al., 2010).

While the exact cognitive processes underlying the P3 remain under debate, a commonly accepted view is that it reflects stimulus evaluation and categorization with respect to the task context (Donchin & Coles, 1988; Luck, 2005), which in turn informs initiation of the task-appropriate stimulus response (Patel & Azzam, 2005). In tasks that require participants to maintain and readily switch between competing stimulus-response schema from trial to trial (e.g., for the SART, due to the unpredictability of the stimulus type) each stimulus must be categorized (e.g., as “go” or “no-go”) and compared against on-line schema (“press to go”, “withhold to no-go”) to decide on the correct behaviour. The P3 is thus associated with both selective and inhibitory aspects of attention over the course of such tasks (Stuss, et al., 1995). Its latency appears to reflect the timing of these cognitive/evaluative processes (McCarthy & Donchin, 1981) while its amplitude reflects their intensity (Kok, 2001). Amplitude appears to relate more reliably to behavioural indices of executive attention (Segalowitz, Dywan, & Unsal, 1997). Within subjects, trial-by-trial performance indices link greater P3 amplitudes to more successful goal-driven task behaviour (Datta, et al., 2007; Smallwood, Beach, Schooler, & Handy, 2008). Between subjects, participants with poorer executive control due to individual differences, aging, or brain injury (that reduce functional network efficiency) show reduced mean P3 amplitudes (Adrover-Roig & Barceló, 2010; Datta, et al., 2007; Segalowitz, et al., 1997). Consistent with the link between arousal and attention (Chennu & Bekinschtein, 2012; Coull, 1998; Posner & Peterson, 1990; Sturm, et al., 1999), P3 amplitude has also been related to phasic activity in the locus coeruleus – norepinephrine system that contributes to cortical arousal (Nieuwenhuis, Aston-Jones, & Cohen, 2005).

The P3 may therefore be used as a neurophysiological metric of both within- and between-subject executive control including attentional allocation and task engagement. In go/no-go tasks, including the SART, emphasis has been on ERP comparisons of trial type. These studies
have shown larger amplitudes and longer latencies in N2 and P3 components on no-go compared to go trials, with a fronto-central P3 peak on no-go trials and parietal P3 peak on go trials (Garavan, et al., 2002; Key, Dove, & Maguire, 2005; Zordan, Sarlo, & Stablum, 2008). In such tasks, no-go trials are rare (i.e. low probability) but also engage conflict monitoring and inhibitory control with concomitant increase in supervisory attention to respond to the task demand (Braver, Barch, Gray, Molfese, & Snyder, 2001; MacDonald, et al., 2000). It is therefore likely that the “no-go P3” reflects an additive effect of probability and attentional allocation (see Johnson (1986) for a similar argument) with combined frontal and parietal sources.

A key advantage of the ERP technique over the common functional neuroimaging methods of PET and now fMRI is its high temporal resolution, which makes it uniquely useful in studying fluctuations in attention during task performance. Sustained attention research may therefore also use the P3 to track lapses and reengagement of supervisory attention over time. During the SART, for example, P3 amplitudes are lower on go trials immediately preceding commission (no-go) errors compared to successfully inhibited no-go “stops” (Datta, et al., 2007). This amplitude effect is paralleled by subjective reports (in response to interjected probes) of transient “mind wandering” off task (Smallwood, et al., 2008; Smallwood, et al., 2004). Differences in P3 amplitude for trials following commission errors compared to stops have received less study though one might expect that reengagement of supervisory attention following an error would be accompanied by post-error increase in P3 amplitude.

ERPs related to error processing are also relevant to the study of executive control as detecting and correcting performance errors are central to successful goal-driven behavioural monitoring and adjustment. Research across several tasks has shown a negative voltage deflection following response errors, typically within 100 ms post-response and with peak amplitudes over fronto-central sites (Van Veen & Carter, 2002a; Yeung, Botvinick, & Cohen, 2004). The primary neural sources of this “error (related) negativity” (ERN/Ne; Falkenstein, Hohnsbein, Hoorman, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) appear to be the medial PFC and caudal ACC (Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004; Van Veen & Carter, 2002a, 2002b) though it may also be affected by white matter integrity within more posterior cingulate (Westlye, Walhovd, Bjørnerud, Due-Tønnessen, & Fjell, 2009).
Originally attributed to conscious error detection (Falkenstein, et al., 1991), the ERN has more recently been explained as reflecting conflict monitoring between competing response schema (Van Veen & Carter, 2002a; Yeung, et al., 2004), e.g. “press to digits other than 3” versus “withhold to 3” on the SART. The relation of ERN to subjective error awareness has been variable across studies (Debener, et al., 2005; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001), though a recent review attributed this to variations in the methods used and threshold of “certainty” required of participants to report making a response error (Wessel, 2011). Wessel concluded that the response/conflict monitoring process that produces the ERN is a significant contributor, together with other sources (e.g. autonomic reactions, Hajcak, McDonald, & Simons, 2003), to subsequent error awareness and behavioural correction. Whether it reflects conscious or pre-conscious error detection, ERN amplitude has been reliably associated with better executive and attentional control during task performance, including post-error slowing (PES) of response speed (Debener, et al., 2005; Gehring, et al., 1993) and fewer response errors (Hajcak, et al., 2003; Westlye, et al., 2009).

A positive voltage deflection may also be observed following the ERN, typically peaking between 200-400 ms post-response. Its occurrence is not as reliable as that of the ERN, that is, it does not always appear as a visible component in error-related waveforms. However, when it does appear, this “error positivity” (Pe; Falkenstein, et al., 1991) has been more reliably related to subjective error awareness compared to the ERN (Hajcak, et al., 2003; Nieuwenhuis, et al., 2001; O'Connell, et al., 2007; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). The centro-parietal Pe maximum found in most studies has been most consistently linked to activity in ACC (overlapping or posterior to ERN sources) and, like the ERN, possibly posterior cingulate (O'Connell, et al., 2007). With both Pe amplitude and post-error autonomic responses linked to error awareness (O'Connell, et al., 2007), the Pe may reflect affective processing within ACC (Bush, Luu, & Posner, 2000) and a subjective, affective error evaluation process (Hajcak, et al., 2003; Herrmann, et al., 2004; Van Veen & Carter, 2002b) that indexes the motivational significance of performance errors (Overbeek, et al., 2005).

The later post-error onset of the Pe relative to the ERN may better allow integration of post-error information (including autonomic responses) sufficient to more reliably cross the “threshold” into conscious error awareness (O'Connell, et al., 2007; Wessel, 2011). Consistent with the relation between awareness and arousal (Laureys, Boly, Moonen, & Maquet, 2009), amplitude of
the Pe (but not the ERN) was linked to global arousal as measured by the ratio of tonic slow- to fast-wave spectral EEG activity (i.e. alpha/beta and theta/beta, O'Connell, et al., 2007). Patient populations with impaired arousal also tend to be less conscious of performance errors (Larson & Perlstein, 2009; McAvinue, O’Keeffe, McMackin, & Robertson, 2005) and have been found to have reduced Pe amplitudes (Larson & Perlstein, 2009), providing one important avenue for impaired self-regulation. In the neurologically healthy brain, Pe amplitude predicts subsequent behavioural correction, typically measured as post-error slowing (Nieuwenhuis, et al., 2001), though without necessarily leading to improved task accuracy (Hajcak, et al., 2003).

1.2 Mindfulness

Meditation is central to many religious and spiritual practices, especially those with Eastern origins. Within Buddhism, Vipassana meditation techniques aim to foster insight into the nature of the mind through present-moment awareness of its content (Hart, 1987). This may include, for example, mindful awareness of bodily sensations and the emotions with which they associate. Over the past few decades, mindfulness meditation practices have become increasingly recognized in both Western popular culture and in the domains of clinical and, more recently, cognitive and neuropsychology.

Much of this may be traced back to the introduction of Mindfulness-Based Stress Reduction (MBSR), a structured, usually group-based treatment program initially developed to assist in the management of chronic pain in oncology patients (Kabat-Zinn, 1982, 1990). The “mindfulness” practice in MBSR has two core aspects: (1) learning self-regulation of attention by sustaining focus to one’s present-moment experience including thoughts, bodily sensation and emotions, and (2) developing an orientation to this experience that is open, accepting and non-judgmental (Bishop, et al., 2004; Kabat-Zinn, 1990). Cancer, and indeed any medical condition that includes chronic pain and prognostic uncertainty or likely deterioration, can produce significant psychological comorbidity including depression and anxiety. In reaction, patients may adopt a repressive or avoidant coping style which, while possibly adaptive in the short-term (e.g., by allowing hope and time to adjust), over time tends to increase psychological and behavioural difficulties (Roth & Cohen, 1986). This can lead to a spiral of worsening in both physical and psychological well-being (e.g., increased experience of pain and depression) as well as reducing patients’ sense of self-efficacy and inhibiting their ability to seek out and pursue effective means
of relief (Grossman, Niemann, Schmidt, & Walach, 2004). By encouraging participants to become more actively engaged in and accepting of the reality of their experience, the assumption is that mindfulness practice may, over time, improve the accuracy of patients’ perceptions of their illness as well as promoting more adaptive coping strategies. MBSR has been used to reduce psychological symptoms secondary to disorders including fibromyalgia, various cancers, coronary artery disease and chronic pain conditions as well as psychiatric disorders including eating disorders, depression and anxiety (Grossman, et al., 2004). Improvements have been reported in psychological health (e.g., improved mood, quality of life and adaptive coping) and – where included in outcome assessments – in physical health (e.g., reduced pain, improved mobility, stronger immune functioning) and health-enhancing behaviours (e.g., reduced substance use and over-eating, improved sleep hygiene) (Greeson, 2009; Grossman, et al., 2004). The psychosocial (and physical health) effects of mindfulness have thus received much study, with increasingly widespread application of MBSR and offshoots including Mindfulness-Based Cognitive Therapy (MBCT) for major depressive disorder (Segal, Williams, & Teasdale, 2002).

Interest is now growing as to the neurocognitive effects of mindfulness training, particularly in relation to its focus on the self-directed regulation of attention. Studies of long-term mindfulness practitioners have reported both structural and functional effects relevant to executive and attentional control. Lazar and colleagues (2005) observed a dose-dependent correlation between mindfulness practice and cortical thickness in areas associated with processing both external (occipito-temporal cortex) and internal (anterior insula) perceptions as well as executive control (lateral PFC), all with the right hemisphere dominance associated with the sustained attention network (O'Connor, et al., 2011; Pardo, et al., 1991; Posner & Peterson, 1990). By appearing to offset the age-related PFC and insular thinning seen in non-practicing age-matched controls, such results suggest that regular mindfulness practice could potentially reduce or delay the loss of executive control that is seen in normal aging. Brefczynski-Lewis, Davidson and colleagues (2007) found greater fMRI activation in long-term mindfulness practitioners (compared to novice meditators) during sustained attentional focus on an unchanging visual stimulus in both “sources” and “sites” of attention, bilaterally in lateral PFC and parietal cortex, thalamus, basal ganglia and cerebellum as well as occipital cortex. Sampling “experienced” practitioners with considerably more practice hours than those in the Lazar study, Brefczynski-Lewis and colleagues observed an inverted-U rather than infinitely linear dose-dependent relation: practiced
meditators with the least experience (LHEMs) showed greater activation in attentional network areas than did those with the most experience (MHEMs). The BOLD timecourse showed that whereas DLPFC activation in MHEMs peaked at the onset of the visual fixation task and then tapered (with activation sustained in visual processing areas) in LHEMs DLPFC was maintained throughout fixation. This was interpreted as increased efficiency in the attentional network after accumulation of extensive mindfulness practice (Brefczynski-Lewis, et al., 2007). This increase in executive-attentional network efficiency dovetails with findings that EEG recordings from long-term practitioners show greater resting cortical arousal (defined as gamma/theta ratio) over fronto-parietal sites, with an additional boost in gamma power and thalamo-cortical synchronization during active meditation (Lutz, Greischar, Rawlings, Ricard, & Davidson, 2004). Further, experienced meditators show reduced P3 amplitudes to task-irrelevant distractor stimuli (Cahn & Polich, 2009). Together with a recent review of studies comparing performance of experienced and novice meditators on attention and executive functioning tests (Chiesa, Calati, & Serretti, 2011), these studies, while retrospective, suggest improved integration and efficiency in executive-attentional networks with accumulated mindfulness practice.

More recent studies have investigated the effects of mindfulness prospectively, assigning novice participants to programs of mindfulness meditation training and practice. These effects would be expected to center on executive control of attention, specifically: (1) sustained attention to the on-going stream of experience; (2) attentional switching to exert control over one’s focus of attention; (3) inhibition of elaborative processing to reduce judgment or rumination that are outside the present moment of experience (which may be viewed as interference suppression); and (4) non-directed attention (attentional scope) broadened to absorb more information from one’s current experience (Anderson, Lau, Segal, & Bishop, 2007; Bishop, et al., 2004). A recent review highlighted the relative paucity of studies investigating objective cognitive effects of mindfulness practice (as compared to self-reported, affective, physical and/or quality of life improvements), and many of these suffer from methodological limitations (Chiesa, et al., 2011). Nonetheless, improved attentional control (switching and interference suppression) has been seen in several trials of mindful meditation training (Jha, Krompinger, & Baime, 2007; Ortner, Kilner, & Zelazo, 2007; Tang, et al., 2007; Wenk-Sormaz, 2005) though effects following MBSR have been less consistent (Anderson, et al., 2007; Jha, et al., 2007). Anderson and colleagues reported no attention effects apart from reduced attentional biasing / greater non-
directed attention, consistent with increased openness to present experience; Jha and colleagues reported improved conflict monitoring. The latter study also reported better receptive attention following 30 days of intensive mindfulness practice in a retreat setting (though this was in a meditation-experienced group that also demonstrated greater executive control at baseline).

Following a similar but shorter (10 day) retreat, novices showed improved sustained attention and attentional switching as well as increased working memory capacity (Chambers, Lo, & Allen, 2008). As with most studies, participants also reported improved mindfulness and affect, here with a moderate correlation to improved attentional switching.

There is early evidence associating these cognitive improvements with changes in executive-attentional neural substrates even over the course of relatively short-term training. In comparison to a resting state, a brief protocol to induce mindful focus on the sensations of breathing was linked to increased activity in anterior cingulate, medial prefrontal and parietal substrates of attentional control, with the right hemisphere dominance typical of sustained attention, as well as bilateral insula (Dickenson, Berkman, Arch, & Lieberman, 2012). These findings are consistent with sustained, goal-directed attention to the sensations of breathing and dovetail with the findings of greater cortical thickness in these substrates in experienced mindfulness practitioners (Lazar, et al., 2005). When asked to maintain focus on scanner sounds during fMRI, increased functional connectivity within auditory (and visual) networks and between auditory cortex and parietal and anterior cingulate regions associated with goal-directed attention were seen following MBSR relative to a wait-list control group (Kilpatrick, et al., 2011). These results were accompanied by decreased connectivity between the visual and auditory networks and between visual cortex and the executive attentional network that further suggested greater efficiency in goal-directed attention to auditory input by reducing task-irrelevant visual processing. ERP studies have also shown prospective effects of mindfulness practice on the attention-related P3 component. Moore and colleagues (2012) studied the effects of group-based instruction in mindful breath focus followed by at least 10 minutes of individual daily practice for 16 weeks, with testing at baseline, mid-point and after 16 weeks on self-report measures and an EEG Stroop paradigm. Though Stroop behavioural performance was not significantly altered in the meditation group (compared to a wait-list control group), they did show attenuation of the P3 component to incongruent stimuli (after 16 though not yet at 8 weeks), suggesting improved
capacity for task-directed control of attentional resource allocation and consistent with results previously shown in experienced practitioners (Cahn & Polich, 2009).

The cognitive and neuroplastic effects seen with mindfulness training in neurologically healthy individuals have spurred interest in expanding trials to neurological, dysexecutive populations (Green & Turner, 2010). There remains, however, a significant lack of research in this area. In an uncontrolled trial in adults and adolescents with attention-deficit hyperactivity disorder (ADHD), patients attended 8 group-based weekly training sessions with daily independent practice using 5-15 minute guided audio recordings (Zylowska, et al., 2008). Pre-to-post training improvements were reported on measures of attentional switching and interference suppression as well as self-reported ADHD symptoms related to inattention. There was, however, no comparison condition to control for test practice or placebo effects and the authors noted a need for replication in a controlled trial. A small-sample pilot study in TBI patients with 4 weekly training sessions and daily practice with guided recordings resulted in improved self-reported executive-attentional functioning and mood, with trends for improvement on cognitive testing (McMillan, Robertson, Brock, & Chorlton, 2002). However, these results were not replicated in a larger randomized controlled trial (RCT), wherein the mindfulness-training and physical exercise control groups both self-reported cognitive improvement but showed no significant change on objective testing.

In interpreting this lack of significant effect, McMillan and colleagues (2002) noted that more extensive supervised practice may be necessary to achieve reliable benefits from mindfulness techniques in TBI patients, though also recognizing this is unfeasible in many clinical settings. Another possibility lies in recognizing the limited ability shown by many dysexecutive patients to independently or spontaneously utilize or transfer newly learned strategies. This suggests an alternate approach of explicitly pairing mindfulness training with guidance and practice in its application to daily activities in order to promote more effective and generalized use of residual attentional control. This approach was investigated in this dissertation research project through the integration of mindfulness techniques in a strategy training program (described in greater detail at the end of this chapter and in Chapter 3) aimed at improving self-regulation of attention and behaviour in patients’ daily activities.
1.3 Distributed brain injury

The distributed networks supporting sustained attention and executive control are vulnerable to damage in either their cortical (e.g., frontal) or subcortical nodes or in the white matter pathways that link these nodes into functional networks. Age-related declines in executive functioning and performance stability have been linked to white matter atrophy and reduced functional connectivity (Campbell, et al., 2012; Charlton, et al., 2006; Fjell, et al., 2011). More pronounced executive dysfunction is seen in pathologies with more extensive distributed damage, including traumatic brain injury (TBI), ischemic white matter disease (Black, Gao, & Bilbao, 2009) and MS. Patients with this type of damage are characterized by slowed information processing and executive dysfunction, as rapid transmission and interregional integration of information are limited by diffuse white matter injury (DWMI). The extent of DWMI in these patients is apparent in measures of reduced parenchymal volumes, which correlate with neurological signs of injury severity as well as executive and self-regulatory dysfunction (Benedict, et al., 2007; Ge, 2006; Levine, et al., 2002). TBI and MS may also produce focal cortical or subcortical cell body lesions causing further region-specific effects. However, DWMI and white matter atrophy alone are sufficient to disrupt the reliable, efficient operation of integrated neural networks that support attention and executive control (Benedict, Bruce, et al., 2006; Dineen, et al., 2009; Mesulam, 1990; Stuss, et al., 1989; Turner & Levine, 2008).

While patients typically retain some function in these networks and therefore some capacity for controlled, attentive behavior, they are vulnerable to distraction and, similar to patients with focal frontal damage (Stuss, Murphy, Binns, & Alexander, 2003), are inconsistent in task performance (Stuss, Pogue, Buckle, & Bondar, 1994). Patients who retain some ability to perform in the “normal” range on high-demand laboratory tasks do so at the apparent cost of increased recruitment in executive control regions (Richard, et al., 2010; Turner & Levine, 2008; Turner, McIntosh, & Levine, 2011). For example, whereas neurologically healthy controls are seen to activate the putative right-lateralized sustained attention network during the SART (O’Connor, et al., 2011), TBI patients with DWMI (and no focal lesions) recruited anterior cingulate and superior medial prefrontal regions (Richard, et al., 2010) that are more typical of high response conflict and demand for inhibitory control (Bunge, et al., 2001; Menon, et al., 2001) and suggest an elevated level of performance monitoring is required by these patients to support behaviour (MacDonald, et al., 2000; Ridderinkhof, et al., 2004). Also similar to patients...
with focal frontal damage (Stuss, et al., 2002), patients with DWMI may show impaired ability to focus and sustain attention on task-relevant information (Stuss, et al., 1989). This results in relatively simple tasks being performed inefficiently, using executive processing substrates (that are not required by neurologically healthy controls) to maintain a “normal” level of task performance at relatively lower levels of task demand (Raja, Tisserand, Stuss, McIntosh, & Levine, 2011; Richard, Levine, O’Connor, & Robertson, in preparation; Turner, et al., 2011).

For example, TBI patients showed activity in lateral prefrontal and anterior cingulate regions on a simple RT task (a perceptual-motor comparison task for the SART in which all trials were “Go”) that was not seen in healthy controls (Richard, et al., in preparation). In the context of both high and low task demand, augmented or compensatory neural recruitment used by patients with DWMI and executive deficits to support behavioural performance is a likely contributor to patient fatigue (DeLuca, Genova, Hillary, & Wylie, 2008; Turner & Levine, 2008) and inability to remain consistently on task (Stuss, et al., 2003; Stuss, et al., 1989). Study of TBI patients has linked this performance variability to lower P3 amplitudes, with both attributable to poorer executive control of attention (Segalowitz, et al., 1997).

1.4 Multiple sclerosis

Multiple sclerosis (MS) is a chronic, progressive central nervous system disease characterized by distributed inflammation, demyelination, gliosis and axonal degeneration. With onset on average between 20 and 40 years of age, it is the third most common cause of neurological disability in adults aged 18-50 (Khan, Turner-Stokes, Ng, & Kilpatrick, 2007). Prevalence is particularly high in Canada where 55,000-75,000 patients have MS (Multiple Sclerosis Society of Canada, 2005), with direct and indirect costs estimated at nearly $1 billion annually (Canadian Institute for Health Information, 2007). MS-related disability can significantly restrict occupational activities (Amato, Ponziani, Siracusa, & Sorbi, 2001; Bobholz & Rao, 2003) and associates with reduced quality of life, mood disturbance and increased risk of suicide (Benito-León, Morales, & Rivera-Navarro, 2002; Chiaravalloti & DeLuca, 2008; Ghaffar & Feinstein, 2007; Janardhan & Bakshi, 2002).

1.4.1 Aetiology and pathology of MS

MS was recognized as a distinct neurological entity over 150 years ago, with descriptions of its symptoms and pathological findings emerging even earlier (Compston, 1988). Despite this long
history, the pathogenesis of MS remains incompletely understood. While a model of MS as a circulatory disorder (Zamboni, et al., 2009) recently garnered attention and continues to be under study (Zivadinov, et al., 2011), historically and currently MS has been defined as an autoimmune disorder in which one or several environmental factor(s) interact with genetic susceptibility. The risk of developing MS increases as the degree of genetic material shared with an affected individual increases, from a 0.3% risk in the general population to around 30% for monozygotic twins of individuals with MS (Compston & Coles, 2008). Both susceptibility and protective genes have been identified, most within the immune-related major histocompatibility complex of the genome (Hafler, et al., 2007; Ramagopalan, et al., 2007). Sex-related genes are also relevant as the modulatory effect of sex hormones on immune activity may explain the greater incidence of MS (approximately 3:1 overall) in females compared to males (Whitacre, 2001). Environmental factors have also been studied as triggers or modifiers of genetic risk, including cigarette-smoking, lack of sunlight/vitamin D deficiency (which may underlie the higher incidence of MS at greater geographical latitudes), and viral infection (Levin, et al., 2003; Marrie, 2004; Munger, et al., 2004; Orton, et al., 2006). Epstein-Barr infection in young adults increases the risk of developing MS, possibly owing to molecular similarity between the Epstein-Barr virus and myelin basic protein (Lang, et al., 2002; Levin, et al., 2003).

1.4.1.1 Diagnosis

Diagnosis of MS is typically made on the basis of the “McDonald criteria”: identification or indication of central nervous system (CNS) lesions disseminated in space and time (McDonald, et al., 2001; Polman, et al., 2005). There are few MS-specific neurological symptoms; in most cases diagnosis is made from a history of transient symptoms or signs indicating involvement of two or more neurological sites (e.g. in motor, somatosensory or visual systems). Gadolinium-enhanced or T2 structural MRI, cerebrospinal fluid analysis for immunological markers, and/or visual evoked potentials may be used to confirm a diagnosis. Typically, physical symptoms (e.g. motor, somatosensory or visual losses) are emphasized in diagnosis as well as neurological ratings of disability (e.g. using the Expanded Disability Severity Scale (EDSS), Kurtzke, 1983). This is likely owing to both the immediate and tangible effects of such symptoms for patients and to the nature of the neurological exam. As will be discussed in a later section, however, the frequency and impact of cognitive symptoms are increasingly recognized.
There are three commonly recognized diagnostic subtypes of MS: relapsing-remitting, primary progressive and secondary progressive. Roughly 80% of patients experience an initial episode of symptoms involving one or several CNS sites. When this initial “clinically isolated syndrome” is followed by a second episode the formal diagnosis of “relapsing-remitting MS” (RRMS) may be made. For 50% of patients this occurs within 2 years following the first attack; the rate of symptom relapses varies considerably but rarely exceeds 1-2 attacks per year (Compston & Coles, 2008). Between relapses, the patient’s functioning is (theoretically) stable. Over time, however, this “remission” tends to become incomplete as patients are left with stable and lasting if relatively milder symptoms (e.g. residual tingling or weakness in a leg that during the acute episode was unusable). A majority of patients with an initially relapsing-remitting course will eventually convert to “secondary progressive MS” (SPMS), defined as a progressive decrease in functioning which may or may not continue to be interspersed with acute symptom relapses or occasional plateaus (Lublin & Reingold, 1996). This transition in clinical course has been largely attributed to accumulated axonal damage and degeneration (Bjartmar, Kidd, & Ransohoff, 2001). The exact proportion of RRMS patients reaching this diagnosis and the time to conversion vary by reports. Until recently, it appeared that approximately 50% of RRMS patients would convert to SPMS within 10 years and 80-90% by 25 years (Burks & Johnson, 2000). Newer data report a considerably slower rate of progression, with 50% conversion (using the same diagnostic criteria) at closer to 19 years (Tremlett, Yinshan, & Devonshire, 2008). This may reflect both imprecision in the clinical distinction between advanced RRMS and SPMS as well as effects of disease-modifying drugs that have been in use since the mid-1990s and which, by reducing the rate and severity of relapses experienced by RRMS patients, should in theory be slowing the accumulation of axonal damage. Finally, around 20% of all MS patients present with progressive symptoms without episodic “attacks” from the onset and receive the diagnosis of “primary progressive MS” (PPMS). The mean age at diagnosis of both PPMS and SPMS is later than for RRMS, at around 40 years (Confavreux & Vukusic, 2006). PPMS and SPMS patients characteristically present with evidence of accumulated DWMI that may also be accompanied by distributed cortical lesions (Kutzelnigg, et al., 2005; Sadatipour, Greer, & Pender, 1998; Stadelmann & Brück, 2008).

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3 numbers vary somewhat by source
1.4.1.2 Pathogenesis

Evidence to date suggests that MS begins with the migration of autoreactive T-lymphocytes across the blood-brain barrier. The trigger for this, as noted earlier, is not entirely clear though may in some cases be linked to systemic viral infection. Genetic susceptibility is expressed as failures in local immunoregulatory processes within the CNS (Viglietta, Baecher-Allan, Weiner, & Hafler, 2004) that allow for “pockets” of auto-immune attack on perivascular myelin. The resulting inflammatory demyelinating lesions cluster around the lateral ventricles and corpus callosum, cortex and subcortical white matter, optic nerves, brainstem and spinal cord (Compston & Coles, 2008). Concentrated immune activity within these acute lesions also causes axonal damage (Ferguson, Matyszak, Esiri, & Perry, 1997; Trapp, et al., 1998). Immune activity fades out from the centre of these lesions into border areas of normal-appearing white matter (NAWM) in which upregulated oligodendrocytes compete with proinflammatory microglia (Kutzelnigg, et al., 2005; Zeis, Graumann, Reynolds, & Schaeren-Wiemers, 2008); adjacent cortex may also be damaged (Magliozzi, et al., 2007). Particularly in earlier stages of the disease, these inflammatory episodes may be asymptomatic.

Following resolution of the acute inflammation – through natural processes or corticosteroid treatment – some degree of remyelination may occur from perilesional oligodendrite precursors (Chandran, et al., 2008; Scolding, et al., 1998; Wolswijk, 1998). Unfortunately, residual inflammatory activity can interfere with this process (Owens, 2003). There is also variability between patients in the extent of recovery that may reflect some underlying pathological heterogeneity (Stadelmann & Brück, 2008). For example, patients lacking expression of ciliary neurotrophic factor (which promotes oligodendrite growth and survival) may show accelerated disease progression (Giess, et al., 2002). Furthermore, axonal damage appears to be irreversible (Freedman, 2011; Rovaris, et al., 2005), cumulative and characteristic of both SPMS and PPMS (Kutzelnigg, et al., 2005; Sadatipour, et al., 1998).

1.4.1.3 Disease progression

As MS progresses, neural connectivity is increasingly disrupted by recurring inflammation, demyelination and axonal injury. In addition to acute inflammatory injury, chronic progressive axonal degeneration occurs both within and distal to lesion sites, from loss of trophic support, local disturbances including edema and gliosis, mitochondrial failure and retrograde or Wallerian
degeneration (Coleman, 2005; De Stefano, Guidi, Stromillo, Bartolozzi, & Federico, 2003; Lassmann, van Horssen, & Mahad, 2012; Su, Banker, Bourdette, & Forte, 2009; Wilkins, Chandran, & Compston, 2001). Progressive axonal damage appears to occur from the time of disease onset (Dalton, et al., 2002; Kuhlmann, Lingfeld, Bitsch, Schuchardt, & Brück, 2002; Rudick, Fisher, Lee, Simon, & Jacobs, 1999) and is believed to be the major source of accumulating permanent disability with disease progression (Bjartmar, et al., 2001; Compston & Coles, 2008; Owens, 2003). This distributed damage eventually gives rise to motor, perceptual, cognitive, and/or socio-emotional dysfunction, with inter-patient variability but commonly affecting corticospinal and thalamocortical tracts and the cognitive domains (e.g. executive control and sustained attention) that rely most heavily on distributed networks (Kolasinski, et al., 2012; Rocca, et al., 2012; Urbanek, et al., 2010).

Several indicators of disease progression in MS are distinguishable on structural MRI and may be used to inform diagnosis. Acute inflammatory lesions of sufficient size are visible with gadolinium enhancement (McFarland, et al., 1992). Sclerotic plaques (permanent lesions) are visible as hypointensities on T1-weighted or hyperintensities on T2-weighted MRI and can be quantified to index local or total lesion volumes (Bodini, et al., 2011; Khoury, et al., 1994; Truyen, et al., 1996). However, much of the progressive neurodegeneration in MS is not visible (at currently available neuroimaging resolutions) in discrete lesions; measures of regional and total volume loss (atrophy) appear to relate more closely with disability (Benedict, et al., 2004; Camp, et al., 1999; Rudick, Lee, Nakamura, & Fisher, 2009; Shiee, et al., 2012) as well as being sensitive to the partial neuroprotective effects of disease-modifying drugs (Rudick, et al., 1999). Axonal damage can also be quantified in normal-appearing white matter (NAWM) using MR spectroscopy (MRS) and diffusion tensor imaging (DTI) (Bar-Or, Rieckmann, Traboulsee, & Yong, 2011; De Stefano, et al., 2003). Tau protein in cerebrospinal fluid – associated with injury severity, neurodegeneration and poor prognosis in other brain disorders (Magnoni, et al., 2012; Shaw, et al., 2009) – has also shown sensitivity to disease progression in MS (Jaworski, Psujek, Janczarek, Szczerbo-Trojanowska, & Bartosik-Psujek, 2012). As with atrophy, these measures of neuronal injury seem more predictive of disability, including cognitive impairment, than are lesion volumes (Bjartmar & Trapp, 2001; Gonen & Grossman, 2000; Mathiesen, et al., 2006) however both lesion volumes and atrophy measures (particularly within white matter) correlate
with clinical deterioration (e.g. EDSS ratings, Caramanos, Francis, Narayanan, Lapierre, & Arnold, 2012; Ge, et al., 2000).

Progressive DWMI, which includes microlesions in NAWM, creates progressive disability in MS by interfering with ascending and descending CNS pathways as well as intracortical functional connectivity. Several studies have highlighted this reduction in neural network efficiency (Loitfelder, et al., 2012; Rocca, et al., 2012) and interregional coherence (Cover, et al., 2006; Leocani, et al., 2000). To date, most of this research has used resting state paradigms. However, task-based neuroimaging has shown converging evidence, with broader activity – to achieve similar behavioural performance levels – compared to neurologically healthy controls that may reflect compensatory activation and/or disinhibition (Audoin, et al., 2003; Cifelli & Matthews, 2002; Mainero, Pantano, Caramia, & Pozzilli, 2006; Tomassini, et al., 2012).

1.4.2 Cognitive impairment in MS

1.4.2.1 Prevalence and functional significance

While heterogeneity in patient sampling and assessment methods have resulted in prevalence estimates ranging from roughly 40-70 %, on average, measurable cognitive impairment occurs in roughly half of all MS patients (Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008; Rao, Leo, Bernardin, & Unverzagt, 1991) and in a majority of patients with PPMS and SPMS (Huijbregts, et al., 2004). The most commonly reported cognitive deficits include slowed information processing speed and impairments in visuospatial perception, supervisory attention and executive functions in addition to aspects of learning and memory (including word retrieval) that are known to be most reliant on attention and executive functions (Anlar, Kisli, Tombul, & Ozbek, 2003; Beatty, 1993; Benedict, Cookfair, et al., 2006; Birnboim & Miller, 2004b; Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008; Huijbregts, Kalkers, de Sonneville, de Groot, & Polman, 2006; Leocani, et al., 2000; Matotek, Saling, Gates, & Sedal, 2001; Rao, 1995; Rendell, Jensen, & Henry, 2007). Sustained attention is impaired (Urbanek, et al., 2010) even in patients with relatively early disease (Crivelli, et al., 2012). As with other DWMI populations, inefficient coordination of executive processes and impaired supervisory attention limit patients’ ability to resist internal and environmental interference. Problem-solving and keeping “on track” with goal-driven activity may become difficult for these patients.
This profile of cognitive impairment can impose far-reaching limitations on MS patients’ participation in daily activities including work, socialization, household responsibilities and driving (Amato, et al., 2001; Benedict, Cookfair, et al., 2006; Bobholz & Rao, 2003; Rao, Leo, Ellington, et al., 1991) as well as participation or adherence to physical therapy and other forms of treatment (Langdon & Thompson, 1999). In addition to this loss of functional independence, psychological well-being and quality of life are often reduced (Benito-León, et al., 2002; Ghaffar & Feinstein, 2007; Haussleiter, Brüne, & Juckel, 2009; Mitchell, et al., 2010; Rao, Leo, Ellington, et al., 1991; Rosti-Otajärvi & Hämäläinen, 2011). A recent systematic review of studies from North America, Australia and Europe estimated the average lifetime costs to the patient and larger economy at $US 1,200,000 per patient, with loss of employment the largest contributing factor (Multiple Sclerosis International Federation, 2010).

1.4.2.2 Neural correlates of cognitive impairment in MS

Cognitive deficits in MS associate with neuroimaging indices of brain atrophy, particularly frontal and parietal white matter atrophy (Bobholz & Rao, 2003; Locatelli, Zivadinov, Grop, & Zorzon, 2004; Piras, et al., 2003), grey matter atrophy (Rudick, et al., 2009), third ventricle volume (Rao, et al., 1985; Sanchez, Nieto, Barroso, Martin, & Hernandez, 2008) and thalamic volume (Houtchens, et al., 2007). As they do not include the DWMI that is present in NAWM, measures of lesion load alone have only modest correlations to cognitive deficit (Bjartmar, et al., 2001; Camp, et al., 1999).

In the early stages of axonal injury in MS, spontaneous neural reorganization and compensatory recruitment may delay functional disability, as shown in the context of relatively preserved motor (Reddy, et al., 2000; Rocca, et al., 2003), visual (Werring, et al., 2000), memory (Hulst, et al., 2012) and executive functioning (Audoin, et al., 2003; Cader, Cifelli, Abu-Omar, Palace, & Matthews, 2006; Loitfelder, et al., 2012; Parry, Scott, Palace, Smith, & Matthews, 2003; Smith, et al., 2009; Staffen, et al., 2002; Wishart, et al., 2004) as well as socio-emotional processing (Passamonti, et al., 2009). Such neuroplastic adaptation may be an additional factor in the modest correlation between visible lesion load and disability (Cifelli & Matthews, 2002; Mainero, et al., 2006). Patients with greater pre-disease “cognitive reserve” (i.e. more efficient and/or adaptive neural connectivity, Stern, 2002) appear to have greater capacity for neuroplastic adaptation to disease progression (Bonnet, et al., 2006). This may delay the onset of measurable
deficits (Sumowski, Chiaravalloti, & DeLuca, 2009) and reduce their severity over the disease course (Sumowski, Chiaravalloti, Leavitt, & DeLuca, 2012). Where capacity for spontaneous adaptation fails, increasingly pronounced cognitive deficits begin to emerge in more advanced, progressive MS with accumulated axonal damage (Lazeron, Rombouts, Scheltens, Polman, & Barkhof, 2004; Mainero, et al., 2006).

One source of motivation for the studies in this dissertation is the hope that improved understanding of neuroplastic mechanisms in MS may lead to interventions that will promote functional recovery (Tomassini, et al., 2012), or at least delay further functional losses.

Compared to structural brain measures, indices of brain functioning including fMRI, EEG and more recently magnetoencephalography (MEG), may afford a clearer understanding of cognitive changes in MS, particularly in the case of subtle impairments and in the context of NAWM (Anlar, et al., 2003; Cover, et al., 2006; Gioia, et al., 2007; Leocani & Comi, 2000; Mainero, et al., 2006; Piras, et al., 2003). Prior to the modern use of MRI, for example, delayed sensory ERPs were instrumental to the diagnosis of MS (Halliday, McDonald, & Mushin, 1973).

Latencies of cognitive ERPs – with most research emphasis on the P3 – are also slowed in MS patients (Aminoff & Goodin, 2001; Honig, Ramsay, & Sheremata, 1992; Triantafyllou, et al., 1992; Vázquez-Marrufo, et al., 2008; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Bramham, et al., 2010). In some cases this evidence of slower cognitive processing can be seen prior to the onset of behavioural impairment, suggesting that ERPs may offer a sensitive yet relatively inexpensive and non-invasive tool to detect early or subclinical cognitive changes (Leocani & Comi, 2000; Linden, 2005; Magnano, Aiello, & Piras, 2006). ERP latencies reflect the timing of cognitive processes and delays would be expected in the context of slowed global information processing due to demyelination and DWMI in MS. ERP amplitudes index the power or intensity of cognitive processes, with scalp voltages reflecting the summation of post-synaptic potentials in underlying cortical neural groupings (Kok, 2001; Luck, 2005). In addition to slower latencies, P3 amplitudes may also be reduced in MS patients compared to neurologically healthy controls (Aminoff & Goodin, 2001; Triantafyllou, et al., 1992; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Bramham, et al., 2010).

In addition to group differences between patients and controls, MS patients with reduced P3 amplitudes (Kiiski, Whelan, et al., 2011; Piras, et al., 2003; Whelan, Lonergan, Kiiski, Nolan,
Kinsella, Hutchinson, et al., 2010) and/or increased P3 latencies (Honig, et al., 1992; Piras, et al., 2003) have shown cognitive impairment on measures sensitive to executive functioning. Within-subjects, these metrics of the P3 appear to be better linked to indices of disease severity and cognitive impairment when elicited in visual as compared to auditory tasks (Kiiski, Reilly, et al., 2011; Piras, et al., 2003; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Hutchinson, et al., 2010). Amplitude and (somewhat less reliably) latency abnormalities in the P3 also appear sensitive to between-subjects disease severity (Ellger, et al., 2002; Honig, et al., 1992) and within-subject disease progression over time (Kiiski, Reilly, et al., 2011; Piras, et al., 2003). They are believed to reflect accumulation of disease-related DWMI and resulting functional disconnection (Honig, et al., 1992; Leocani & Comi, 2000; Magnano, et al., 2006) affecting the P3’s multi-focal sources. Differences in the topographical distribution of the P3 between patients and controls are further suggestive of altered large-scale brain dynamics in the context of MS (Whelan, Lonergan, Kiiski, Nolan, Kinsella, Bramham, et al., 2010).

Direct evidence of neural network dysfunction in MS has been shown with reduced regional specialization on fMRI (Schoonheim & Filippi, 2012; Wishart, et al., 2004) as well as inter-regional coherence on EEG or MEG. Reduced neural coherence, particularly in the alpha frequency range and above, has been correlated to brain atrophy and cognitive dysfunction (Arrondo, et al., 2009; Cover, et al., 2006; Leocani, et al., 2000; Tecchio, et al., 2008). These network studies have emphasized “resting state” paradigms with no task-based demand for integrated neural activity. Similar to recent fMRI studies (Loitfelder, et al., 2012; Rocca, et al., 2012), the available EEG and MEG research has thus begun to explore changes to functional connectivity but with limited study of effective task-based connectivity in the context of DWMI due to MS. Resting state studies offer several advantages (Enzinger & DeLuca, 2012) including minimization of potential confounds from MS patients’ motor issues or from differences in task performance between groups (an important methodical issue in neuroimaging with clinical populations, Price & Friston, 1999). However, there is also a need to better understand how MS patients’ brains react to cognitive demands (e.g. for sustained attention and executive control, Cader, et al., 2006), whether to predict functional outcomes or suggest interventions and design their evaluation.

While there is some evidence of abnormal error-related ERPs in other DWMI populations (Larson, Kaufman, Schmalfuss, & Perlstein, 2007; Larson & Perlstein, 2009), there are no
published investigations of these components in MS. Further, in their reliance on oddball (vigilance) paradigms, for which performance data are rarely provided, the available body of P3 studies has generally failed to examine task-based neurophysiological correlates of controlled attention in MS in direct relation to performance on the scanning task. Doing so could expand the utility of this method to explore cognitive changes and adaptation in MS. In addition, while their sensitivity to disease-related cognitive change and relative ease of administration (compared to fMRI) have suggested ERPs as a valuable candidate tool for evaluating effects of treatment on cognitive functioning (Leocani & Comi, 2000), to my knowledge clinical trials have not capitalized on this potential.

1.4.2.3 Medical management of cognitive symptoms

While the prevalence of cognitive impairment and its impact on MS patients’ daily functioning have been increasingly recognized, these tend not to be thoroughly assessed and are often not readily observable in standard neurological examinations (Benedict & Zivadinov, 2011). Patients’ self-reported cognitive functioning may be confounded by mood, fatigue and other symptoms (Carone, Benedict, Munschauer, Fishman, & Weinstock-Guttman, 2005). Further, given the likelihood of executive dysfunction, patients may lack the insight necessary to appreciate and self-report their cognitive symptoms.

Thanks to disease-modifying agents now available to delay MS progression (Rieckmann, Traboulsee, Devonshire, & Oger, 2008; Wingerchuk, 2008), the onset of cognitive dysfunction associated with accumulated neuronal injury may also be delayed (Bates, 2011; Fischer, et al., 2000; Patti, et al., 2010). Additional agents are commonly used to speed recovery from inflammatory relapses (e.g., high-dose methylprednisolone) and for symptomatic therapy, e.g., for muscle spasticity, pain, fatigue, sexual and urinary difficulties (Beer, Khan, & Kesselring, 2012). Unfortunately, however, disease progression cannot as yet be halted or reversed (Freedman, 2011; Havrdova, et al., 2009), particularly in the progressive, degenerative stages and subtypes of MS (Bar-Or, et al., 2011). Emerging disability, which for many patients will include cognitive dysfunction, can be expected; comprehensive rehabilitation programs, including interventions for cognitive impairment where indicated, are recommended to maintain functional independence, participation levels and associated quality of life (Beer, et al., 2012).
1.5 Cognitive rehabilitation

Spontaneous recovery after acute brain injury as in TBI (Povlishock & Christman, 1995; Povlishock, Erb, & Astruc, 1992) and adaptation in neurodegenerative conditions such as MS (Cifelli & Matthews, 2002; Mainero, et al., 2006) are now well-documented particularly in the context of DWMI. However, especially where the damage is extensive, spontaneous reorganization may result in less than optimally efficient or even maladaptive connectivity (Povlishock & Christman, 1995; Robertson & Murre, 1999; Schoonheim & Filippi, 2012). Further, with more severe or progressive damage, there appears to be a limit to the ability of naturalistic neuroplastic mechanisms to restore or prevent loss of brain function (Lazeron, et al., 2004; Macciocchi, et al., 1993; Mainero, et al., 2006). Given the extensive network nature of executive and attention processes, these are among the most vulnerable to incomplete recovery or progressive impairment in conditions involving DWMI.

Where spontaneous neuroplasticity fails, cognitive rehabilitation protocols may be used to attempt (1) restoration of function in the damaged neurocognitive network (e.g., using residual neighbouring neurons) and/or (2) the learning of compensatory strategies, be they internal (i.e., engaging alternate cognitive processes) and/or external (i.e., using prosthetics such as electronic organizers). A distinction may thus be made between targeting the underlying impairment or working at the level of the behavioural disability (Rohling, Faust, Beverly, & Demakis, 2009; Wilson, 2008). A restorative approach may be especially viable in the context of the partially lesioned circuits accompanying DWMI, using empirically-validated exercises to promote activity along synaptic pathways in the affected neural network (Hebb, 1949) and encourage new dendritic branching to rebuild connectivity (Cifelli & Matthews, 2002; Kolb, 2004; Robertson & Murre, 1999; Tomassini, et al., 2012). As a general rule, however, increasingly extensive injury will limit neural circuit recoverability and therefore require an emphasis on internal and external compensatory approaches (Robertson & Murre, 1999). Some interventions, such as Goal Management Training (GMT; Levine, Robertson, et al., 2000), may include aspects of both approaches to promote maximal behavioural recovery. (This particular intervention is described in greater detail below.)

Several reviews have now demonstrated the potential effectiveness of cognitive rehabilitation across neurological disorders involving focal injury and/or the DWMI pattern characteristic of
TBI and MS. However, the strength of evidence varies considerably by cognitive domain and by approach within each targeted domain (Cicerone, et al., 2005; Levine, Turner, & Stuss, 2008; O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008). In addition to specific effects on the targeted cognitive impairment and/or functional disability, non-specific effects of intervention (e.g., education, peer and therapist support, promotion of active coping strategies) can improve patient quality of life (Rosti-Otajärvi & Hämäläinen, 2011).

1.5.1 Rehabilitation of executive and attentional functions

Cognitive rehabilitation is a relatively young field that has seen exponential growth in published trials within roughly the past three decades. However, perhaps owing to practical constraints in patient sampling and clinical settings, for many cognitive domains there is a relative dearth of randomized controlled trials (RCTs) as recommended to achieve a level of evidence sufficient to inform clinical practice guidelines (Cicerone, et al., 2005; Woolf, 1992). This is particularly true in the domain of executive functioning, where further methodological limitations have included poor definition of the targeted processes, limited or insensitive outcome measures (in part a reflection of the particular challenge of assessment in this area, as described earlier) and lack of investigation into the generalization and durability of treatment effects. For example, reports of success in restoration-oriented computer-based “drill” style “attention (re)training” programs have tended to hinge on performance in tests that are similar to the tasks used for training (Filippi, et al., 2012; Niemann, Ruff, & Baser, 1990; Sohlberg & Mateer, 1987; Sturm, Willmes, Orgass, & Hartje, 1997). In these contexts, treatment effects may be largely limited to practice effects with little or no evidence of benefit to everyday, real-life functioning (Park, Proulx, & Towers, 1999; Ponsford & Willmott, 2004). These problems are compounded by inflation of treatment effect sizes without a comparison group to control for practice effects (Park & Ingles, 2001; Rohling, et al., 2009). As a result of such issues, the most recent available comprehensive reviews concluded that although there are several promising approaches under study – including some thus far explored only in neurologically healthy samples (Dahlin, Neely, Larsson, Bäckman, & Nyberg, 2008; Persson & Reuter-Lorenz, 2008; Tang & Posner, 2009) – there remains no consensus recommendation as to standardized, well-validated cognitive rehabilitation approaches for patients with deficits in executive control, supervisory attention and self-regulation (Cicerone, et al., 2005; Levine, et al., 2008; O'Brien, et al., 2008). There are, however,
several compensatory “strategy-training” approaches that have shown promise (e.g., in small or waitlist-controlled studies); these are reviewed in more detail in the following sections.

1.5.2 Research in MS

Growing recognition of the prevalence and impact of cognitive impairment in MS has stimulated interventional research but the strength of evidence has been limited in many cases by the methodological issues described above with additional patient sampling issues (e.g., heterogeneous samples without appropriate analyses or samples restricted to early or “mild” MS). Within the relatively small executive-attentional cognitive rehabilitation literature, the majority of patient studies have been conducted in TBI or stroke populations (Cicerone, et al., 2000; Cicerone, et al., 2005; Levine, et al., 2008). To the extent these have involved patients with DWMI and resulting cognitive-behavioural profiles that share similarities with MS patients, these studies may still inform MS patient care or at the very least suggest promising approaches for further study.

As in other dysexecutive populations (Levine, et al., 2008), pharmacological approaches to treat cognitive symptoms (as well as disease-modifying agents that may delay symptom progression) have been receiving much study in MS. In MS, these have largely focused on agents aimed at increasing cortical arousal and information processing speed (e.g., dopaminergic and/or noradrenergic releasers or reuptake inhibitors) or improving memory functions (e.g., acetylcholinesterase inhibitors). Results have been mixed (Benedict & Zivadinov, 2011; Patti, 2012).

Despite their generally greater resource requirements compared to drug studies, cognitive rehabilitation studies are also (slowly) being pursued in MS. The first comprehensive review (O’Brien, et al., 2008) identified a total of 16 studies with only four meeting Class I criteria (Cicerone, et al., 2000; Woolf, 1992). Of these, only one (Solari, et al., 2004) targeted executive or attentional processes, using a computer-based training program which did not appear effective. More recent reviews and meta-analysis (Beer, et al., 2012; Rosti-Otajärvi & Hämäläinen, 2011) have highlighted the continued lack of methodological rigour in this literature. A relatively small number of studies have tested several interventions within the most MS-relevant cognitive domains (processing speed, attention, executive functioning, working memory capacity, learning and memory), with null results or small effect sizes. Some studies have offered combined (also known as integrative, holistic or multiple-skills) interventions.
While this approach allows for patient-tailoring (Khan, et al., 2007), it creates difficulty comparing effects across studies to draw conclusions about active components. It may also introduce noise and reduce detection of treatment effects, as these approaches have showed no statistically significant effect upon meta-analysis (Rosti-Otajärvi & Hämäläinen, 2011).

As in research with other populations, benefits to MS patients have been reported in studies of computer-based attention training programs where these have included outcome measures similar to the training tasks and/or had no active control group (Filippi, et al., 2012; Mattioli, Stampatori, Zanotti, Parrinello, & Capra, 2010; Plohmann, et al., 1998). However, in a more rigorous RCT of “memory and attention” training with a “visuo-motor training” control group (using different programs within the RehaCom software package, www.schuhfried.com), Solari and colleagues (2004) found equivalent improvement for both groups on (1) a small number of cognitive tests (measuring verbal and spatial memory, verbal fluency and psychomotor speed; oddly, the authors did not employ well-validated tests of attention) and (2) self-reported mood and quality of life. While improvements were maintained at a 2-month post-treatment follow-up, the authors concluded that the lack of group differences suggested non-specific treatment (i.e., placebo) effects. Patient characteristics, most notably indices of MS type and severity, were poorly specified and were not considered in analyses of treatment effects. It may be the case that inclusion of patients with more severe MS (if this did occur in Solari and colleagues’ sample) influenced the group outcomes; studies reporting success with computer-based attention training have tended to include only patients with RRMS and lower levels of disability (Filippi, et al., 2012; Mattioli, et al., 2010). In a study of computer-based “verbal and working memory” training (again compared to a no-treatment control group), only the patients with less baseline brain atrophy (measured with whole-brain parenchymal fraction) showed some generalization of improvement on tests (of psychomotor speed and working memory) that were not versions of tasks used in the training protocol (Hildebrandt, et al., 2007).

Two other studies could be found that targeted executive-attentional dysfunction in MS. One offered a meta-cognitive training program combining computer- and paper-based “strategy” exercises with supervision to increase awareness of deficits and use of problem-solving strategies (Birnboim & Miller, 2004a). Improvement was seen in both strategy application (suggesting a form of “skills training”, see Park & Ingles, 2001) and on a broader test battery, however similar to Hildebrandt and colleagues (2007) less improvement was seen in patients with more severe
MS (here, SPMS compared to RRMS). These results must be considered preliminary owing to the lack of control group (O'Brien, et al., 2008). Another study combined paper-based “executive function exercises” (the nature of which was unfortunately not further specified) with weekly psychologist feedback and discussion, comparing this “cognitive intervention group” (CIG) to a placebo group (PG) receiving computer-based reaction time training and to a no-treatment control group (Fink, et al., 2010). Post-treatment, faster set shifting and verbal learning were seen in CIG compared to both PG and no-treatment. Compared to the no-treatment group, CIG patients further showed reduced omission errors in a 2-back working memory task, which suggests improvement in sustained attention. Within CIG, a correlation was seen between increased set shifting speed and baseline brain atrophy (whole-brain parenchymal fraction). Its directionality was not entirely clear given the brevity of this report but does, together with other studies, confirm the importance of examining potential effects of disease severity on outcome, even within diagnostic subgroup (all in Fink’s study were RRMS patients). The attenuation of most treatment effects at a one-year follow-up also highlights the importance of exploring the durability of treatment effects.

A small number of more recent studies have begun to include neuroimaging markers of treatment effects, a promising approach with the potential to increase understanding of not just whether an intervention works, but how. For example, in a Class I RCT using fMRI during a word-learning task, MS patients trained to use the modified Story Memory Technique (mSMT; Chiaravalloti, DeLuca, Moore, & Ricker, 2005) showed increased pre-to-post-treatment activation in a network of frontal, parietal and temporal regions previously associated with executive, memory and visual imagery processes (Chiaravalloti, Wylie, Leavitt, & DeLuca, 2012). No change was seen in the placebo control group. Within the mSMT group, behavioural improvement correlated with increased activity in the right DLPFC node. This suggests that use of the mSMT improved patients’ memory by increasing their use of encoding strategies, i.e. by increasing executive control to support memory processes. This intervention may also increase functional connectivity within memory-linked networks involving the hippocampi and posterior cingulate (Leavitt, Wylie, Girgis, DeLuca, & Chiaravalloti, 2012).

In a less methodologically rigorous study, MS patients received computer-assisted training with the RehaCom package (also employed by Solari et al., 2004) compared to a no-treatment control (Filippi, et al., 2012). The patient sample was limited to those with RRMS and indices of less
neurological progression (EDSS < 4, see Kurtzke, 1983) but who nonetheless presented with executive dysfunction as defined by cognitive test performance (on the WCST and PASAT). The specific training tasks consisted of (1) simulated errand-planning (which may represent a form of strategic skills training) and (2) simulated driving with distractions that included performance of a concurrent PASAT-type task. Post-training improvement on the PASAT as well as WCST and verbal fluency was reported for the training group. Using fMRI, the training group showed activation increases in posterior cingulate and DLPFC during incongruent Stroop trials (that depend on selective goal-driven attention and interference suppression, e.g. MacLeod, 1991). These changes correlated with improvement on (unspecified) “attention and executive” tests.

Effects on resting-state functional networks were also reported, with the training group showing pre-to-post-training “stability” as compared to controls’ “decreased fluctuations” in anterior and posterior cingulate, DLPFC and parietal regions. These findings were interpreted as greater network integrity in the training group, particularly with further evidence of increased functional connectivity of the ACC to lateral frontal and parietal regions (in the right hemisphere) specific to the training group (Parisi, et al., 2012). However, the authors’ conclusions that the training program specifically strengthened executive-attentional neural networks must be viewed as tentative given their small sample size and lack of active (placebo) control group.

Overall, it would appear the conclusions of O’Brien and colleagues (2008) still hold: cognitive rehabilitation holds much promise in ameliorating deficits in MS, but methodological issues that are prevalent within the literature limit conclusiveness of most studies to date. As a result, there are, as of yet, no accepted practice standards or guidelines for behavioural or pharmacological treatment of attentional, executive and self-regulatory deficits in patients with MS. In particular, more evidence is needed from studies that (1) include an active (“placebo”) control group; (2) assess outcomes using both (a) cognitive tests validated to measure the treatment-targeted processes and (b) indices of everyday functioning to explore treatment generalization; (3) assess both post-treatment and longer-term effects to explore treatment durability and make clinical recommendations as to follow-up (e.g., need for “booster” sessions); (4) specify and explore the effects of disease severity on outcomes; and ideally (5) explore potential neural correlates of treatment effects using functional measures such as fMRI, MEG or EEG.
1.5.3  Goal Management Training

With the small number of studies available for review, Cicerone and colleagues (2000; 2005) had concluded that training in problem-solving strategies was promising. Such approaches derive from views of problem-solving as a process involving sequential steps, e.g. adopting an active orientation including recognizing the problem, defining the problem and goal state, generating action plans, making the decision and verifying the outcome (D’Zurilla & Goldfried, 1971). As described earlier, patients with executive impairments may have difficulty with any one or several of these steps, resulting in a disorganized and inefficient approach to navigating even basic everyday problem-solving.

One of the key advantages offered by such approaches is the potential for “real-life” functional benefits (Kennedy, et al., 2008) if patients can learn the strategies and develop facility with applying them in their everyday activities. Only one problem-solving / meta-cognitive study (Birnboim & Miller, 2004a) has targeted self-regulatory impairment in patients with MS (Birnboim & Miller, 2004b). While this approach produced pre-to-post improvements in RRMS patients (less so in SPMS patients) on a strategy application test that demands maintenance of goal-directed behaviour (Levine, et al., 1998) as well as tests of attention and memory, these results must also be considered tentative given the lack of control group (O’Brien, et al., 2008).

Von Cramon and colleagues (Von Cramon, Matthes-von Cramon, & Mai, 1991) trained patients with acquired brain injuries (mainly TBI and stroke) to approach problems as a series of smaller, “manageable” steps with techniques for structuring each stage. While the specifics were not provided in much detail, one example of this problem-solving training (PST) included making a list of “pros and cons” for each solution alternative when making the decision. In comparison to an active (mnemonic training) control group, the PST group had improved performance pre-to-post-training on both a standard test of planning (a variant of the Tower test) and a more ecologically valid planning test that was devised to approximate real-life problem-solving by having patients schedule activities and errands within set parameters (e.g. store hours, travel time). Clinician ratings of patients’ everyday problem-solving behaviour as observed in the clinical setting (on an in-house scale developed for the study) also improved only in the PST group, which was interpreted by the authors as evidence of generalization. However, it is not clear from the authors’ report whether the raters were blinded to patients’ group assignment.
Further, the protocol description suggested some variability between patients in the focus and level of therapist interaction. For example, avolitional patients – who have particular difficulty with problem orientation – received additional one-on-one supervision with repeated cueing to stay on task. It was not made clear if such patients ever achieved independent strategy use.

Rath and colleagues (Rath, Simon, Langenbahn, Sherr, & Diller, 2003) explicitly provided training in both problem orientation and substeps of problem-solving for all patients, with the rationale that improving the former (e.g., accepting one’s impairments and improving ability to recognize problem situations) is likely to facilitate use of the latter. However, they also did not describe any of their patients as abulic, suggesting that significant volitional deficits – which seem resistant to behavioural training alone (Marin & Wilkosz, 2005) – were not present in this particular sample. Together the Von Cramon and Rath studies highlight the importance that patients retain some degree of volitional and meta-cognitive ability if they are to engage in strategy training and learn to generalize its application to improve everyday functioning.

In its current version, Goal Management Training (GMT; Robertson, 1996) also begins by increasing patients’ awareness, through education and self-monitoring exercises described in greater detail in Chapter 3, as a critical step to set the stage for strategy learning and application.

The initial “probe” study of GMT was included in Cicerone and colleagues’ (2005) review as the only Class I study targeting executive dysfunction. The content and aims of GMT are grounded in neurocognitive models of executive functioning. These include Mesulam’s (2002) description of executive functions as providing an evaluative space or buffer between input and response, enabling contingent or goal-directed rather than impulse-driven behaviour. GMT is also based on views that executive dysfunction involves lapsed supervisory attention (Norman & Shallice, 1986) during which the goal and its related action set are displaced from working memory, resulting in goal neglect (Duncan, et al., 1996). The distractible, disorganized or habit-driven behaviour typical of dysexecutive patients reflects this loss of goal orientation, with actions becoming stimulus- or impulse-driven rather than goal-directed.

Accordingly, the central aim of GMT is training patients to “stop”, i.e. to temporarily suspend ongoing behaviour. The act of stopping reintroduces a space between input and response, facilitating reassertion of executive control. It is a form of “content-free” cueing, in that it provides no specific task directive or information as, for example, memory cueing techniques.
External content-free cues, such as random alerting tones, have been shown to serve as a prosthetic for sustained attention when participants are instructed to use them as a reminder to consider (i.e., direct their attention towards) their goals and current activity. In neurologically healthy individuals, this cueing reduces demand for endogenous supervisory attention during the SART, as evidenced by reduced activity in the right DLPFC that drives the sustained attention network (O'Connor, et al., 2011). Using the same paradigm to compare SART performance with and without alerting tones in TBI patients, these cues were associated with increased recruitment of right DLPFC and reduced ACC activity (Richard, et al., 2010). Given the differential roles of DLPFC and ACC in self-regulation (Silton, et al., 2010; Van Veen & Carter, 2002a), these findings suggested that (1) compared to controls, TBI patients with DWMI exert greater attention control and response monitoring to maintain SART performance and (2) periodic cueing may help support the otherwise inefficient sustained attention system in such patients. Alerting cues have indeed been shown to improve patients’ ability to remain on task and accomplish goals (Fish, et al., 2007; Manly, et al., 2002; Manly, et al., 2004) reducing the performance variability that is otherwise typical of TBI patients (Stuss, et al., 1989).

While successful at reducing executive dysfunction and goal neglect, for practical reasons the approach of providing patients with external cues may not be ideal as a permanent solution. For example, it would require that patients always carry some electronic device programmable to deliver the alerts. Patients may also find this approach awkward or intrusive in their daily activities, e.g., when in the presence of coworkers or other social environments in which alerts may seem indiscrete. In Goal Management Training, patients learn to gradually internalize the “stop” cue that is initially provided as an external cue by the trainer.

The act of “stopping” is used as the patients’ cue to purposefully redirect their attention to their goals (in working memory) and engage in evaluation of whether their actions are achieving these goals and, if needed, alter their action plan. This is accomplished through a series of steps, with each taught, practiced by patients and combined in sequence over the course of training. In the pilot version of GMT, the steps consisted of: “stopping”; stating (identifying and defining) the goal; breaking the goal or task into steps; developing a firm action plan, and; carrying it out with regular “stopping” to check that one remains on task (Levine, Robertson, et al., 2000). These steps were initially compressed into a single training session intended as a proof-of-principle. In comparison to an equally brief motor-training control condition, this “probe” version of GMT
produced benefit on in-house paper-and-pencil tasks designed to simulate real-life organizational activities. The authors also reported benefits to a trained, real-life task (meal preparation) in a subsequent case study with an extended (2-session) version of GMT and pre-post design. Together these results were considered preliminary but promising (Cicerone, et al., 2005).

The content of GMT has since been expanded and refined by Levine, Robertson and colleagues over a series of trials (Levine, Robertson, et al., 2000; Levine, et al., 2007) including a larger, double-blinded RCT of a 7-session version that introduced greater education and awareness-building as well as mindfulness practice (Levine, et al., 2011). Several other groups have tested GMT or programs derived from GMT adapted to their clinical population and/or outcome of interest (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011; Chen, et al., 2011; Fish, et al., 2007; Grant, Ponsford, & Bennett, 2012; Jackson, et al., 2012; Miotto, Evans, de Lucia, & Scaff, 2009; Novakovic-Agopian, et al., 2011; Stubberud, Langenbahn, Levine, Stanghelle, & Schanke, 2013). Two studies have also suggested GMT as a promising intervention for age-related executive decline. These were somewhat limited in design by virtue of (1) using only a wait-list control condition, in a within-subject crossover (Levine, et al., 2007) or between-groups RCT (van Hooren, et al., 2007), and (2) relying on non-standardized tasks and self-report measures in the assessment of outcome.

Though the available clinical evidence for rehabilitation of executive dysfunction through GMT is limited to smaller group (n < 25) or case studies, improvements on objective, well-validated measures of executive functioning and self-regulation including the SART, Tower Test, Hotel Test, and MET have been seen across patients with frontal as well as non-frontal (e.g., cerebellar) focal lesions (Levine, et al., 2011; Miotto, et al., 2009; Schweizer, et al., 2008), post-acute TBI patients (Grant, et al., 2012; Levine, Robertson, et al., 2000; Novakovic-Agopian, et al., 2011), spina bifida myelomingingocele (SBM) patients (Stubberud, et al., 2013) and patients with executive dysfunction secondary to severe systemic illness (Jackson, et al., 2012) or poly-substance abuse (Alfonso, et al., 2011). Three of these studies have been Class I RCTs with comparison to “standard care” or “placebo” control conditions (Alfonso, et al., 2011; Jackson, et al., 2012; Levine, et al., 2011) and one a RCT with wait-list control (Stubberud, et al., 2013). Two were Class Ia crossover designs with comparison to brief education or “standard care” programs (Miotto, et al., 2009; Novakovic-Agopian, et al., 2011). Where tested, there has been some evidence of secondary improvement in learning and memory (Novakovic-Agopian, et al.,
2011) and of generalization to patients’ daily, “real-life” goal attainment (Grant, et al., 2012; Novakovic-Agopian, et al., 2011). Also where tested, post-GMT improvements have been maintained at follow-up assessments ranging from 1 to 6 months (Levine, et al., 2011; Novakovic-Agopian, et al., 2011; Stubberud, et al., 2013). Effects on self-reported executive functioning have been seen in some studies (Jackson, et al., 2012; Stubberud, Langenbahn, Levine, Stanghelle, & Schanke, in preparation) but not all (Levine, et al., 2011). The latter findings may have partly reflected patients’ tendency to under-report their baseline (pre-training) level of impairment owing to poor awareness (Schweizer, et al., 2008).

Only one published report has looked at neural correlates of treatment (Chen, et al., 2011), in the crossover design study of TBI patients completing a modified version of GMT and an education program (Novakovic-Agopian, et al., 2011). Patients were scanned using fMRI during a 1-back working memory task. Each trial presented both a face and scene, with the instruction to identify repeated faces on some trials but scenes on others, thereby manipulating the task relevance of each stimulus class. From pre-to-post GMT, but not the control condition, patients showed more efficient goal-directed attentional modulation of visual processing in extrastriate cortex, with greater activation for task-relevant compared to distractor stimuli in face- or scene-processing regions according to which were attended. Within the DLPFC sources of attentional control, normalization of activation levels relative to pre-GMT suggested improved capacity for effective representation of the relative task relevance of the stimuli in each trial. One limitation of this study was its lack of examination of direct relations between these neural attentional effects and behavioural performance. The scanning task was designed to be performed at ceiling pre-treatment, and no analyses with the behavioural outcome measures were reported.

As with other interventions designed to teach patients to use strategies to improve their ability to structure and manage complex, non-routine, real-life activities, GMT may be primarily viewed as a compensatory approach aimed at reducing functional disability. That is, instead of repeated practice in specific isolated “attention (re)training” exercises, which have questionable translation to everyday functioning, the focus of GMT is training patients to apply self-regulatory strategies in ecologically valid training tasks with gradual translation and integration into meaningful, real-life situations to enhance patients’ daily functioning. To the extent that GMT incorporates mindfulness techniques to practice attentional control, some reinforcement and restoration of executive-attention-related neural activity could occur, however this is not a
primary aim of the approach. In contrast to attention training protocols that have reported results mainly in less impaired patients – consistent with the neurorehabilitation framework of Robertson and Murre (1999) – GMT has been shown to benefit patients with a wider range of injury severity and impairment, including severe TBI (Grant, et al., 2012; Levine, Robertson, et al., 2000). While not yet explicitly tested in a neurodegenerative population, these findings suggest GMT as a potentially useful intervention for patients with progressive brain disease such as MS.
Chapter 2
Rationale and Hypotheses

Having established that executive functions rely on distributed functional networks and are vulnerable to the DWMI that characterizes MS, that there are as yet no widely accepted treatments for executive dysfunction (either pharmacological or cognitive) validated for use with MS patients, and that GMT has shown positive effects in other clinical or subclinical DWMI populations with executive challenges (aging, TBI), the primary aim of this dissertation was to evaluate GMT as a potential intervention for the amelioration of executive-attentional and self-regulatory impairment in MS patients.

In order to interpret intervention-related effects, it was necessary to first evaluate baseline neurocognitive functioning in the participating MS patients. Part of this first stage of research was relating task- and performance-linked ERPs (the P3, ERN and Pe) to MS patients’ actual task performance as well as broader neuropsychological functioning, thereby addressing a gap in the existing MS literature.

2.1 Combined neurophysiological and behavioural characterization of executive dysfunction in MS

As a marker of attentional allocation, the P3 has recently been used to assess within-task, performance-linked fluctuations in sustained attention in neurologically healthy individuals (Datta, et al., 2007; Smallwood, et al., 2008; Zordan, et al., 2008). As reviewed in Chapter 1 and in contrast to research in TBI (Segalowitz, et al., 1997), this task-linked ERP approach has not yet been extended to the study of attention and attentional impairment in MS. A second cognitive ERP family – the error-related negativity (ERN) and positivity (Pe) – has also been thus far underused in studying the impact of MS on performance monitoring aspects of executive control. Response conflict and error monitoring (as indexed by the ERN and Pe) have been linked to task performance and behavioural self-correction in neurologically healthy participants (Debener, et al., 2005; Gehring, et al., 1993; Hajcak, et al., 2003; Nieuwenhuis, et al., 2001; Westlye, et al., 2009). Evidence for the disruption of these processes by DWMI has recently been found in TBI (Larson & Perlstein, 2009). This study explored the possibility of similar findings in MS.
The first aim of this dissertation was therefore to link cognitive, functional-behavioural, and neurophysiological effects of MS as these relate to sustained attention and executive control, using both within-group (e.g., as a function of disease progression and cognitive impairment) and between-group (e.g., in comparison to neurologically healthy controls) uni- and multivariate analyses (described in Chapter 3). The following specific hypotheses were tested:

1. As a group, MS patients will be impaired on measures of information processing speed and executive functioning including controlled aspects of attention. MS patients will also report greater absentmindedness and executive dysfunction in daily life, corroborated by informant reports if patients retain insight. These cognitive deficits will be independent of verbal intellectual abilities (which will be equivalent to controls).

2. Cross-sectionally within the MS patient group, the presence and severity of executive dysfunction will increase with indicators of disease progression.

3. On the EEG-linked task (the SART, see Chapter 3), behavioural indicators of response conflict resolution (trial accuracy) and performance monitoring (post-error slowing) will be linked to greater amplitudes in the ERN and Pe in both controls and patients with MS.

4. Replicating (with controls) and extending (to MS patients) prior research, the P3 will provide an index of within-subject goal-directed attentional allocation, with greater amplitudes on SART No-go as compared to Go trials.

5. The P3 will also be sensitive to local fluctuations or lapses in sustained attention, with greater amplitudes on (a) correct responses compared to errors particularly on the more attentionally-demanding No-go trials and (b) trials immediately preceding a correct inhibition compared to a No-go error. Amplitude increase from pre-to-post commission errors will relate to post-error behavioural correction (reaction time slowing).

6. Between-subjects, P3 amplitude averaged across correct SART Go and No-go trials will provide an index of sustained attention and relate to response accuracy and stability, extending prior research in both controls and patients.
7. P3 amplitudes will be attenuated in patients compared to controls overall but also specifically associated with patients’ disease severity and severity of cognitive impairment.

2.2 Rehabilitation of executive dysfunction in MS

The primary aim of this dissertation was to conduct a double-blinded randomized controlled trial to evaluate the efficacy of Goal Management Training (GMT) as an intervention for MS patients with impaired sustained attention and executive control. Consistent with Class I study criteria and to control for non-specific and/or practice effects, GMT was compared to an active control group. Both are described in detail in Chapter 3. Briefly, the Brain Health Workshop (BHW) was a psycho-educational program designed to provide levels of participant engagement and program intensity that were comparable to those of GMT. While BHW and similar psycho-educational programs may increase patients’ awareness of cognitive impairment (here, in relation to MS), they provide no specific tools to help patients compensate for them.

Outcomes both immediately post-training and at 6-month follow-up were compared for GMT and BHW. Cognitive ERPs (P3, ERN and Pe) were used to investigate changes in neurocognitive processing in conjunction with change on cognitive and functional-behavioural measures. The following specific hypotheses were tested:

1. GMT will have a greater effect than BHW on improving sustained attention and executive control as measured by the SART and neuropsychological outcome battery including functional-behavioural measures (e.g., success in goal attainment).

2. Self-rated daily functioning will improve in both groups but, as a typically more objective measure, informant-rated daily functioning will improve more in GMT patients.

3. ERPs will prove useful as a relatively inexpensive and accessible measure of changes in neural activity following cognitive rehabilitation. Specifically, the behavioural effects of GMT on performance of the EEG task (the SART) as well as broader cognitive outcome tests will be coupled to changes in cognitive, task-based ERPs, including:

   a. increased mean P3 amplitude with behavioural indicators of improved attentional control (on the SART, TEA and Hotel Test);
b. increased ERN amplitude with improved resolution of response conflicts (e.g., reduced No-go errors) and improved performance monitoring (e.g., reduced reaction speed and variability) on the SART and broader battery;

c. increased Pe amplitude with improved behavioural self-correction (post-error slowing on the SART).

4. Both GMT and BHW patients will report improved mood and sleep quality due to non-specific benefits (e.g., social support, trainer interaction) provided by both programs.

5. Owing to the compensatory orientation of GMT, intervention effects will be seen in patients across the range of disease severity included in the sample, i.e. for patients in both relapsing-remitting and progressive stages of MS.
Chapter 3
Methods

3.1 Participants

All research activities satisfied the Tri-Council Policy Statement (TCPS2) guidelines (2010) and were approved by institutional ethics review at Baycrest Centre for Geriatric Care (Baycrest) and Sunnybrook Health Sciences Centre (SHSC) in Toronto, Ontario, Canada. All participants were recruited through one of these institutions, as described below and in Section 3.4.1.

For participating in the first part of the dissertation research program (characterization, with neurophysiological correlates, of sustained attention and executive functioning in people with MS), inclusion criteria were: (1) age 18 or older; (2) fluent in English; (3) able to provide informed consent to all procedures; (4) no history of developmental disorder; (5) neither history of nor current substance abuse; (6) diagnosis of MS with no concurrent or previous neurological disorder; (7) no psychiatric disorder (other than mood, personality, or behaviour change following the onset of MS); (8) no other medical condition suspected to influence cognition; (9) no current benzodiazepine or neuroleptic medication use; (10) no relapse during the study period or the two months prior; (11) sufficient motor and sensory functioning (e.g., as determined by neurological examination, with an Expanded Disability Severity Scale (EDSS; Kurtzke, 1983) score ≤ 8) – with correction or assistance as required – to complete assessment activities; and (12) preliminary indication of functionally significant attention or executive deficits (e.g., from clinical presentation, chart information from the referring institutional clinic and/or patient self-report). Aside from the medications listed above (excluded for their effects on EEG), patients were not excluded for undergoing treatment for MS or concurrent mood disorder, but were asked to report any change in treatment status. (No changes were reported during the study period).

To continue participating in the second study (the cognitive rehabilitation RCT), patients met the following additional inclusion criteria: (13) objective evidence of functionally significant attention or executive deficits (as determined by the baseline neuropsychological evaluation); (14) ability to complete all study activities, including attendance at 9 weekly training sessions, individual progress meetings and post-training assessments; and (15) sufficient arousal capacity, awareness of deficits and motivation to engage in the interventions. Though patients were not
excluded for reported mood disturbance, correlational analyses were used to evaluate the potential impact of baseline mood disturbance on patient outcome measures.

As there are no widely accepted stand-alone measures that reliably capture criterion 15, each patient was evaluated on a combination of chart information from the referring institutional clinic, performance and behaviour during the baseline neuropsychological evaluation, clinical opinion, and/or patients’ self-report. Patients were not excluded on the basis of disease-related or symptom-management medication regimens provided these were in accordance with standard medical care. For patients who continued their participation into the rehabilitation trial, test results from the first part of the study were used as their functional baseline, and compared to post-training and 6-month-followup results on the outcome assessment battery (see Table 1 and Section 3.4) to evaluate invention effects.

Based on prior rehabilitation (with an emphasis on GMT) research, a conservative estimate of a small effect size (0.2) was entered into a statistical a priori power analysis using G*Power-3 software (Faul, Erdfelder, Lang, & Buchner, 2007). For power (1-β) = .9 with two intervention groups (GMT, BHW), three repeated-measurement time points (baseline, post-training, 6-month follow-up) and an interest in both main and interaction effects of intervention (treatment) and time (with α = .05), the calculated sample size was N = 24. Recognizing the possibility of attrition over the course of the study, MS patients were enrolled until 28 patients had entered the intervention RCT (14 in each of the GMT and BHW programs).

A sample of 10 neurologically healthy controls, matched to the MS patients for age, education, and male-to-female ratio, were recruited through the Rotman Research Institute at Baycrest. Inclusion criteria were: (1) age 18 or older; (2) fluent in English; (3) able to provide informed consent to all procedures; (4) no history of developmental disorder; (5) neither history of nor current substance abuse; (6) no neurological, psychiatric, or other medical condition suspected to influence cognition; and (7) no current benzodiazepine or neuroleptic medication use.

In accordance with institutional ethical guidelines, all participants were provided financial compensation for their time and travel expenses to/from the Rotman Research Institute at Baycrest which was the site of all research activities. Participants who began but did not complete the study in its entirety were provided compensation proportional to their participation.
time. All MS patients participating in Study 1 (baseline assessment) were also offered the option of having a brief neuropsychological report of their test results sent to their referring MS clinic.

3.2 Materials

To thoroughly characterize participants’ baseline level of functioning and investigate cognitive, functional-behavioural, and neurophysiological effects of intervention, multiple measures were used to span levels of functional description as recommended in the International Classification of Functioning, Disability and Health (World Health Organization, 2001). Assessment thus included MS patients’ neurocognitive changes or impairment as well as the impact of these on both laboratory-simulated and real-life daily activities and behaviour.

3.2.1 Neuropsychological measures: Cognitive, behavioural and functional

A battery of neuropsychological tests (Table 1) was used to describe the sample of MS patients (and neurologically healthy controls) in terms of processing speed, attention, executive functions, visuospatial and basic verbal abilities. Based on administration and reference materials for these tests including authoritative texts on neuropsychological assessment (Lezak, et al., 2004; Strauss, Sherman, & Spreen, 2006), the major cognitive domains and processes tapped by each measure are listed in Tables 1 and 5. Reference materials (Table 1) describe psychometric properties including reliability for all measures as being within conventionally acceptable limits.

A subset of these cognitive tests, together with functional-behavioural and self-report measures, was used to assess outcomes post-intervention and at a 6-month follow-up (Tables 1 and 5). Many of the tests in this battery have been used – or were similar to tests that have been used – in prior rehabilitation research including GMT studies (Grant, et al., 2012; Jackson, et al., 2012; Levine, et al., 2011; Levine, et al., 2007; Novakovic-Agopian, et al., 2011; Stubberud, et al., 2013) and were selected for having previously demonstrated sensitivity to the executive-attentional effects of GMT in other populations. For example, within the Test of Everyday Attention, selected subtests (2-5) were used to assess sustained attention (TEA-2: Elevator Counting [auditory]), selective attention including interference suppression (TEA-3: Elevator Counting with Distraction [auditory]) and attentional switching (TEA-4 [visual] and TEA-5 [auditory]: Elevator Counting with Reversal).
<table>
<thead>
<tr>
<th>Test †</th>
<th>Primary Domain(s) ‡</th>
<th>Administration Schedule ±</th>
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<tbody>
<tr>
<td><strong>Cognitive Tests</strong></td>
<td></td>
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<tr>
<td>DKEFS Tower Test</td>
<td>Planning; working memory (EF)</td>
<td>MS1-3</td>
</tr>
<tr>
<td>Trail Making Test (A/B)</td>
<td>Psychomotor speed; visual scanning; attention (EF)</td>
<td>MS1-3</td>
</tr>
<tr>
<td>JLO *</td>
<td>Visuo-spatial perception</td>
<td>MS1</td>
</tr>
<tr>
<td>PASAT (3.0 &amp; 2.0 s ISI) *$</td>
<td>Processing speed; attention; working memory (EF)</td>
<td>MS1</td>
</tr>
<tr>
<td>SART</td>
<td>Sustained attention; inhibitory control (EF)</td>
<td>MS1-3</td>
</tr>
<tr>
<td>SDMT *</td>
<td>Processing &amp; psychomotor speed; visual scanning</td>
<td>MS1</td>
</tr>
<tr>
<td>SILS Vocabulary Test (“Shipley”)</td>
<td>Estimated general intellectual ability (verbal)</td>
<td>MS1</td>
</tr>
<tr>
<td>TEA (Elevator subtests 2-5)</td>
<td>Attention (selective, switching, sustained) (EF)</td>
<td>MS1-3</td>
</tr>
<tr>
<td>Verbal Fluency (FAS) *</td>
<td>Language; strategic memory retrieval (EF)</td>
<td>MS1</td>
</tr>
<tr>
<td>WAIS-III Digit Span</td>
<td>Attention; working memory span</td>
<td>MS1</td>
</tr>
<tr>
<td><strong>Functional-Behavioural Measures</strong></td>
<td></td>
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<tr>
<td>GAS</td>
<td>Success and satisfaction with goal attainment (change scores) (“real-life” EF)</td>
<td>MS1-2</td>
</tr>
<tr>
<td>Hotel Test</td>
<td>Monitoring; attention; prospective memory (EF)</td>
<td>MS1-3</td>
</tr>
<tr>
<td><strong>Self-Report Measures</strong></td>
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<tr>
<td>CFQ</td>
<td>Absentmindedness in everyday life (“real-life” EF)</td>
<td>MS1-3</td>
</tr>
<tr>
<td>DEX</td>
<td>Occurrence and impact of executive function deficits in everyday life; insight (“real-life” EF)</td>
<td>MS1-3</td>
</tr>
<tr>
<td>POMS</td>
<td>Mood (tension-anxiety, depression, anger-hostility, vigour-activity, fatigue, confusion-bewilderment)</td>
<td>MS1-3</td>
</tr>
<tr>
<td>PSQI</td>
<td>Sleep quality</td>
<td>MS1-3</td>
</tr>
</tbody>
</table>

† CFQ = Cognitive Failures Questionnaire (Broadbent, et al., 1982); FAS (Spreen & Benton, 1977; Strauss, et al., 2006); DEX = Dysexecutive Questionnaire (Wilson, et al., 1996); DKEFS = Delis-Kaplan Executive Function Scale (Delis, et al., 2001); GAS = Goal Attainment Scaling (Kiresuk, et al., 1994); JLO = Judgment of Line Orientation (Benton, 1994; Benton, Sivan, Hamsher, Varney, & Spreen, 1994); PASAT = Paced Auditory Serial Addition Test (Gronwall, 1977; Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989); POMS = Profile of Mood States (McNair, Lorr, & Droppleman, 1992); PSQI = Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989); SART = Sustained Attention to Response Task (Robertson, et al., 1997); SDMT = Symbol Digit Modalities Test (Smith, 1982); SILS = Shipley Institute of Living Scale (Shipley, 1991); TEA = Test of Everyday Attention (Robertson, et al., 1996b); WAIS-III = Wechsler Adult Intelligence Scale (3rd ed.) (Wechsler, 1997).

$ This slower version of the PASAT (Rao et al., 1989) has become standard when assessing MS patients, to reduce confounding from slower global processing speed when using this task to evaluate executive processes.

‡ As described in test administration and reference material and/or neuropsychological compendiums (Lezak, et al., 2004; Strauss, et al., 2006). “Selective attention” here includes interference suppression. “Attention switching” includes cognitive / mental flexibility. EF = executive functioning.

± C = test administered to neurologically healthy Control subjects; MS1 = test used to describe sample of MS patients and administered only at time 1 (pre-training); MS1-3 = test used to assess treatment outcome, administered to MS patients at time 1 (pre-training), time 2 (post-training), and time 3 (6 months post-training), with the exception of GAS which was not administered at the 6-month follow-up.
Within the cognitive tests, the Sustained Attention to Response Task (SART; Robertson, et al., 1997) comprised the primary outcome measure and was linked to neurophysiological activity as recorded by EEG. The EEG parameters are described below (Sections 3.2.2 and 3.3.2).

Behaviourally, five key indices were obtained from the SART. These were calculated as follows. The proportion of errors on each trial type (Go, No-go) was calculated to give the percentage of trials that constituted errors of omission (failure to respond on Go trials) and errors of commission (failure to inhibit response on No-go trials). Correct No-go trials are hereafter referred to as “Stops” whereas failed No-go trials are commission “Errors”. The mean reaction time (RT) across correct Go trials was calculated as an index of overall response speed. The coefficient of variation of reaction time (cvRT = mean RT / standard deviation of RT) was calculated as an index of performance stability. Finally, the difference in RT between (correct) Go trials preceding and following No-go Errors was calculated as an index of self-monitoring and behavioural adaptation (“post-error slowing”). To increase reliability, RTs were averaged from the three trials preceding and three trials following No-go Errors.

Self ratings on the Cognitive Failures Questionnaire (CFQ; Broadbent et al., 1982) together with self and informant ratings on the Dysexecutive Questionnaire (DEX; Wilson et al., 1996) were used to assess each participant’s tendency to “absent-mindedness” and the impact of executive dysfunction in his or her daily life. DEX items were grouped to obtain scores on five component dimensions – Inhibition, Intention, Executive Memory, Positive Affect (i.e., emotional lability) and Negative Affect (i.e., emotional blunting) – as well as a Total Score (Burgess, et al., 1998). Each participant nominated one informant (a close friend or family member, preferably one cohabiting with the participant, where possible) to complete a parallel (“other”) form of the DEX rating scale. The degree of corroboration between DEX “self” and “other” ratings provides an estimate of the participant’s level of insight as to the presence, severity and impact of executive dysfunction; patients with poor insight will tend to report significantly fewer difficulties than are identified by their informants (e.g., Schweizer et al., 2008).

Measures related to participant quality of life involved mood and sleep quality. Mood was assessed through participants’ self-endorsement of items on the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992) with scores obtained for six component mood dimensions – Tension-Anxiety, Dejection-Depression, Anger-Hostility, Vigour-Activity, Fatigue-Inertia and Confusion-Bewilderment – as well as a Total Mood Disturbance score. Sleep quality was
assessed with the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), combining information about relevant aspects of sleep (e.g., difficulty falling asleep, need for sleep medication) into a Global Score indexing overall sleep disturbance.

Functional-behavioural measures included the Hotel Test (Manly, et al., 2002) and Goal Attainment Scaling (GAS; Kiresuk, Smith, & Cardillo, 1994). The Hotel Test is a modified version of the Six Elements’ Test (Shallice & Burgess, 1991) and provides an ecologically valid (Burgess, et al., 2006) simulation of a “multi-tasking” work environment. Participants were given materials for five clerical tasks (compiling bills, sorting money, looking up phone numbers, sorting name tags and proof reading a pamphlet) and a prospective memory task (pressing a button to “open” and then to “close” a “garage door” at pre-specified times) and were asked to attempt some of each task while pretending to “run a hotel” for 15 minutes. Per the usual administration for this test, a clock was provided to allow patients to monitor their time on task and for timing responses for the garage door task. Scores derived for the Hotel Test reflect participants’ goal awareness, self-monitoring and attentional control and included: (1) the number of clerical tasks attempted (out of the instructed five); (2) deviation from the optimal time one should spend on each task (3 minutes) given the overall goal of attempting each task in the allotted total test time; and (3) deviation from the instructed “garage door” times, expressed as a score from 0 (failing to push the button at all) to 8 (pressing the buttons within 60 seconds of both instructed times) per the scoring criteria for this test (Manly, et al., 2002).

GAS was used as a rehabilitation outcome measure and not administered to the neurologically healthy controls. As part of their baseline assessment, all MS patients were asked to choose two real-life examples of their functional challenges and to set goals for their improvement. As needed, patients’ goal definition was guided by the trained research assistant doing the assessments to ensure that goals pertained to executive-attentional functioning and were “SMART”, i.e. specific, measurable, attainable, relevant and time-bound (Bovend’Eerdt, Botell, & Wade, 2009). Examples of goals chosen by patients in this study are listed in Table 2. For each goal, patients identified their current state as the “baseline” (i.e., “-2” on the goal attainment scale). Increments on each patient’s goal scales were then filled in with a “target” (assigned a “0” value) as well as an “ideal” state (assigned a “+2” value). Each level on the scale was set in reference to the target activity, supporting action required and performance metric, creating a series of states ranging from the current undesirable state (“-2”) through the state the participant
targeted as acceptable ("0") to a state that would exceed the participant’s expectations ("+2"). Examples of completed goal attainment scales are also included in Table 2.

Table 2. Examples of participant goal attainment scaling (GAS)

<table>
<thead>
<tr>
<th>Scale Value</th>
<th>SMART Goal State (activity, actions, performance)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example # 1</strong></td>
<td>For a patient with multiple medications to coordinate:</td>
</tr>
<tr>
<td>Current</td>
<td>-2 Habitually losing track of medications, has to rely on husband for reminders</td>
</tr>
<tr>
<td></td>
<td>-1 Start a medication record, limit confusion / checking with husband / errors to 3-4 times per week</td>
</tr>
<tr>
<td>Target</td>
<td>0 Use a medication record, limit confusion / checking with husband / errors to 1-2 times per week</td>
</tr>
<tr>
<td></td>
<td>+1 Use a medication record, limit confusion / checking with husband / errors to 1 time every 2 weeks</td>
</tr>
<tr>
<td>Ideal</td>
<td>+2 Use a medication record, fully self-sufficient with no errors</td>
</tr>
<tr>
<td><strong>Example # 2</strong></td>
<td>For a patient who is employed (telecommuting) in a job requiring extensive reading:</td>
</tr>
<tr>
<td>Current</td>
<td>-2 Unable to remain focused on work for periods longer than 5-10 minutes</td>
</tr>
<tr>
<td></td>
<td>-1 Start a timer with intention to focus on work, remain focused for up to 15 minutes at a time</td>
</tr>
<tr>
<td>Target</td>
<td>0 Use a timer to measure work period, remain focused for 15-30 minutes at a time</td>
</tr>
<tr>
<td></td>
<td>+1 Use a timer to measure work period, remain focused for 30-45 minutes at a time</td>
</tr>
<tr>
<td>Ideal</td>
<td>+2 Use a timer to measure work period, able to remain focused for &gt; 45 minutes without distraction</td>
</tr>
<tr>
<td><strong>Example # 3</strong></td>
<td>For a patient who is the primary homemaker (responsibilities including taking children to school, most household shopping, meal preparation, etc.):</td>
</tr>
<tr>
<td>Current</td>
<td>-2 Forgetting items at home when leaving (e.g. child’s lunch) or forgetting to complete an errand before returning home nearly every day</td>
</tr>
<tr>
<td></td>
<td>-1 Start using a “to-do” list, remember to bring all items and complete all errands for the day at least 1 day per week</td>
</tr>
<tr>
<td>Target</td>
<td>0 Use a “to-do” list, remember to bring all items and complete all errands for the day on 2-3 days per week</td>
</tr>
<tr>
<td></td>
<td>+1 Use a “to-do” list, remember to bring all items and complete all errands for the day on 4-5 days per week</td>
</tr>
<tr>
<td>Ideal</td>
<td>+2 Use a “to-do” list and remembering to bring all items and complete all errands for the day on more than 5 days per week, minimal forgetting</td>
</tr>
</tbody>
</table>

Patients assigned to GMT chose one of these goals as an “individual project” to work and report on during the 9-week training, thereby providing a specific and on-going real-life context in which to apply GMT skills as they were learned. Progress on the remaining goal was simply assessed post-training, as were both goals for patients in the BHW group. The GAS procedure with SMART goal-setting is increasingly used in rehabilitation settings and is sensitive to
clinically significant rehabilitation progress in persons with MS (Khan, Pallant, & Turner-Stokes, 2008) though it has thus far been underused in cognitive rehabilitation research.

### 3.2.2 Neurophysiological measures: Event-related potentials

EEG, specifically the ERP technique, was used to (1) augment description of neurocognitive functioning in relation to executive-attentional processes as seen in the participating MS patients, and (2) investigate outcome at the neural level following patients’ participation in the GMT and BHW programs.

#### 3.2.2.1 Experimental paradigm

Participants completed two tasks during EEG data acquisition. The SART (Robertson, et al., 1997) was the main task of interest. Single digits (1 through 9) were sequentially presented at a central fixation point (ITI = 1150 ms, with a 900 ms mask between digits) in random order. Participants were asked to respond to all digits except the number ‘3’ by pressing the spacebar on a lap-mounted keyboard with the preferred hand. Participants were instructed to withhold a response when presented with the digit ‘3’. The probability of these No-go trials was 11%. The SART was administered in 5 blocks, each lasting approximately 4.3 minutes and containing 200 Go trials (digits 1-2 and 4-9) and 25 No-go trials (digit 3). To minimize fatigue, SART blocks were interspersed with 60-second blocks of passive visual fixation of a standard reversing checkerboard stimulus (Odom, et al., 2004) in the order: SART1, SART2, checkerboard1, SART3, SART4, checkerboard2, SART5. (Data from the passive checkerboard task will be analyzed separately and are not included in this dissertation.)

#### 3.2.2.2 Data acquisition

EEG data were acquired in a soundproofed room using the ActiveTwo system (Biosemi B.V., Netherlands) with a 66-channel head cap (organized according to an extended 10/20 system) plus five pairs of flat electrodes for a total of 76 recording sites (see Appendix 1). The flat electrodes included two pairs of ocular sites to monitor vertical and horizontal eye movements from the outer canthi and infra-orbital ridges (IO1, IO2, LO1, LO2), one pair situated over the mastoids (TP9/TP10), and two pairs of facial electrodes (FT9, FT10, F9, F10). Continuous EEG was recorded at a 512 Hz sampling rate using Cz as the reference. DC offset was kept below the
manufacturer recommended 40 mV for all electrodes (Smith, 2009); the majority (90%) of electrodes across participants had offsets < 20 mV.

At the start of the EEG session, participants were trained to minimize ocular contamination (blinks and lateral movements) through completion of eye movement exercises with feedback from the experimenter (Picton, van Roon, et al., 2000). Participants also completed a practice run of the SART to ensure understanding of the task instructions prior to administration of the SART and reversing-checkerboard blocks.

3.2.3 Rehabilitation programs

Both the GMT program and its experimental control, the BHW program, were designed to be highly interactive, combining lectures on key topics with discussions relating to participants’ experiences with in-class activities and homework. The GMT program focused on information and activities to build skills in goal awareness, attentional control and self-regulation, while providing a socially supportive atmosphere to practice and discuss progress with these skills. The BHW program contained information and activities to increase participants’ knowledge of brain function, cognition and MS, while providing social support and lifestyle recommendations (e.g., energy conservation, nutrition and exercise, stress reduction). Detailed outlines of the 9 modules comprising the GMT and BHW programs are given in Tables 3 and 4 respectively.

3.2.3.1 Goal Management Training

The GMT program administered in this trial was adapted from the 7-module format used in our research group’s most recent trial with other clinical populations (Levine, et al., 2011). For this dissertation, administration was expanded to 9 group-based modules to (1) give additional discussion time to material from some of the original modules and (2) increase the mindfulness component. The earlier version of GMT introduced mindfulness mid-way through the program. In the current study, mindfulness or “present-mindedness” was introduced as a key concept from the first session as a foundation for patients to build awareness of variability in their own attentional states, e.g. contrasting mindfulness with mind wandering or “absentmindedness”.

Both within-session and as homework, participants engaged in a set of “present-mindedness” exercises aimed at gradually building attentional awareness and control. These were modeled on widely used mindfulness techniques (Dickenson, et al., 2012; Kabat-Zinn, 1982; Moore, et al.,
2012; Segal, et al., 2002), with instructional emphasis on (1) becoming aware of attentional lapses or “mind wandering” and (2) without further elaboration or judgment, redirecting attention back to the focus or goal of the exercise, e.g., the sensations that accompany natural breathing as well as other aspects of the participant’s immediate experience including thoughts, feelings or external events. This approach integrated models of supervisory attention and executive functioning with the conceptualization of mindfulness as a combination of attentional regulation and non-judgmental openness to experience (Bishop, et al., 2004).

This ongoing mindfulness practice, with a focus on breathing exercises, was integrated with key GMT strategies (e.g., “stopping the autopilot”, “checking the mental blackboard”, see Figure 1). The GMT program thus embedded mindfulness techniques within (1) accessible education about executive functions, including attention and working memory, (2) building self-awareness of when and why “slips” (errors, forgetfulness) occur, (3) self-regulatory strategies learned in the context of functional tasks and participants’ daily life situations, and (4) training in the use of compensatory aids (organizers, mnemonics) within the overall self-regulatory strategy training. The aim was for a manualized (and therefore translatable) intervention for executive dysfunction that was also tailored to participant needs and real-life challenges.

### 3.2.3.2 Brain Health Workshop

The BHW was a psycho-educational program about the brain, cognition and functional changes associated with MS. It was modeled after the psycho-educational programs that appear to be – where anything is provided – a standard approach for cognitively impaired populations (e.g., TBI survivors) in medical and rehabilitation settings (including those in which this author completed clinical practica). Unlike GMT or other targeted cognitive rehabilitation protocols, such psycho-educational programs may increase patients’ awareness of potential cognitive deficits but do not provide specific tools to help patients compensate for deficits or achieve functional gains.

The BHW program combined education about various domains of cognition, their relation to brain functioning and potential effects of MS. In order to achieve a level of participant-centered discussion and personal relevance that was comparable to the GMT program, considerable time was spent on group discussions of participants’ experiences related to the topic material. Homework assignments were also designed to be comparable in terms of length and involvement to those within the GMT program. BHW assignments included relevant readings (that were
included in the next session’s discussions), sets of “brain challenge” exercises (e.g., word games, mazes, math puzzles) similar to those included in popular “brain fitness” materials, self-assessment scales and log-keeping.

**Table 3. Outline of Goal Management Training (GMT) sessions**

<table>
<thead>
<tr>
<th>Session</th>
<th>Key Concepts</th>
<th>Within-Session Exercises</th>
<th>Between-Session Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. The Absent / Present Mind</strong></td>
<td>Introductions</td>
<td>Warm-up / Introductions exercise</td>
<td>Self-monitoring I: Log instances when you were absentminded or forgetful</td>
</tr>
<tr>
<td></td>
<td></td>
<td>What are goals?</td>
<td>Self-monitoring II: Log practice of present-mindedness (PM) in daily activities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effects of MS and objectives of GMT</td>
<td>Remember to bring workbook to next session</td>
</tr>
<tr>
<td></td>
<td>Introduction to the Mental Laboratory</td>
<td>Tapping (Clapping) Task</td>
<td></td>
</tr>
<tr>
<td></td>
<td>What is absentmindedness?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Learning to self-monitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>What is present-mindedness?</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present-mindedness I: Practicing everyday activities with present-mindedness</td>
<td>Trying an everyday activity with present-mindedness: The raisin exercise</td>
<td></td>
</tr>
<tr>
<td><strong>2. Absentminded Slip-ups</strong></td>
<td>Absentmindedness and slip-ups</td>
<td>Rating absentmindedness</td>
<td>Log Slips (with situational factors and consequences)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tapping (Clapping) Task - revisited</td>
<td>Log daily PM practice: Body Scan</td>
</tr>
<tr>
<td></td>
<td>Slips and intelligence</td>
<td></td>
<td>Remember to bring workbook to next session</td>
</tr>
<tr>
<td></td>
<td>Consequences of slips</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>What makes slips more/less likely: Personal and situational factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present-mindedness II: Focusing attention (the Body Scan)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Present-mindedness: Body Scan exercise (20 minutes)</td>
<td></td>
</tr>
<tr>
<td><strong>3. The Automatic Pilot</strong></td>
<td>The Automatic Pilot</td>
<td>Card-Dealing Task</td>
<td>Log Slips (with situation factors [were you on autopilot?] and consequences)</td>
</tr>
<tr>
<td></td>
<td>Being on automatic pilot can lead to errors, slips and unintended consequences</td>
<td></td>
<td>Log daily PM practice: Breathing exercise (10-20 minutes) and Body Scan (alternate days)</td>
</tr>
<tr>
<td></td>
<td>Being present-minded is the opposite of being on automatic pilot</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present-mindedness III: Focusing attention (the Breathing Exercise)</td>
<td>Present-mindedness: Breathing exercise (10 minutes)</td>
<td></td>
</tr>
<tr>
<td><strong>Individual appointment with Trainer to discuss program progress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. STOPping the Automatic Pilot</strong></td>
<td>Stopping the automatic pilot: Options considered</td>
<td>Tapping (Clapping) Task with &quot;STOP!&quot;</td>
<td>Log Slips (note situational factors [were you on autopilot?] and consequences)</td>
</tr>
<tr>
<td></td>
<td>Using &quot;STOP!&quot; to get out of automatic pilot</td>
<td>Card-Dealing Task with &quot;STOP!&quot; by Trainer</td>
<td>Log 30-minute daily &quot;STOP!&quot; practice</td>
</tr>
<tr>
<td></td>
<td>Present-mindedness IV: Focusing attention quickly (the 3-minute Breath Focus)</td>
<td>Card-Dealing Task with &quot;STOP!&quot; by Participant</td>
<td>Log daily PM practice: Breath Focus (set 3x daily)</td>
</tr>
<tr>
<td>5. The Mental Blackboard</td>
<td>Card-Dealing Task with &quot;STOP!&quot; by Participant - revisited</td>
<td>Log Slips AND Successes (focus on strategies used and consequences)</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Using &quot;STOP!&quot; to (re)direct attention and check the mental blackboard</td>
<td>Card-Dealing Task with distraction</td>
<td>Log 30-minute daily practice: &quot;STOP!&quot; → Breath Focus → Check mental blackboard</td>
<td></td>
</tr>
<tr>
<td><em>Integrating skills/concepts learned to date:</em></td>
<td>Breath Focus (3 minutes)</td>
<td>Log daily PM practice: Breathing exercise (10-20 minutes)</td>
<td></td>
</tr>
<tr>
<td>&quot;STOP!&quot; → Present-mindedness (Breath Focus) → Check mental blackboard</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Stating Your Goal</th>
<th>Complex Task I</th>
<th>Log Slips and Successes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Being sidetracked from your goal</td>
<td>Complex Task II (using STOP-STATE)</td>
<td>Log 30-minute daily practice: STOP-STATE cycle</td>
</tr>
<tr>
<td>How we remember things: Mnemonic strategies</td>
<td>Complex Task III (using a To-Do List)</td>
<td>Log daily PM practice: Breathing exercise</td>
</tr>
<tr>
<td>State (and restate) your goal</td>
<td></td>
<td>Get an organizer to make TO-DO lists</td>
</tr>
<tr>
<td><em>Integrating skills/concepts learned to date:</em> The STOP-STATE cycle:</td>
<td></td>
<td>Catalogue task I with STOP-STATE</td>
</tr>
<tr>
<td>&quot;STOP!&quot; → Present-mindedness (Breath Focus) → Check mental blackboard → (Re)State your goal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Individual appointment with Trainer to discuss program progress**

<table>
<thead>
<tr>
<th>7. Making Decisions</th>
<th>Complex Task III (using a To-Do List)</th>
<th>Log daily STOP!-Focus-STATE practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal conflicts</td>
<td>Complex Task III (using a To-Do List)</td>
<td>Log daily PM practice: Breathing exercise</td>
</tr>
<tr>
<td>Emotional reactions to conflicting goals</td>
<td>Complex Task III (using a To-Do List)</td>
<td>Get an organizer to make TO-DO lists</td>
</tr>
<tr>
<td>To-Do Lists in the STOP-STATE cycle</td>
<td>Complex Task III (using a To-Do List)</td>
<td>Catalogue task I with STOP-STATE</td>
</tr>
<tr>
<td>Indecision</td>
<td>Complex Task III (using a To-Do List)</td>
<td></td>
</tr>
<tr>
<td>Solving indecision: Strategies</td>
<td>Complex Task III (using a To-Do List)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. Splitting Tasks into Subtasks</th>
<th>Complex Task III (using a To-Do List)</th>
<th>Log daily STOP!-Focus-Check practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling overwhelmed</td>
<td>Complex Task III (using a To-Do List)</td>
<td>Log daily PM practice: Breathing exercise</td>
</tr>
<tr>
<td>Tasks and Subtasks:</td>
<td>Complex Task III (using a To-Do List)</td>
<td>Log STOP-STATE-SPLIT scenarios</td>
</tr>
<tr>
<td>Splitting the task up</td>
<td>Complex Task III (using a To-Do List)</td>
<td>Catalogue tasks II and III with STOP-STATE-SPLIT</td>
</tr>
<tr>
<td><em>Integrating skills/concepts learned to date:</em> The STOP-STATE-SPLIT cycle:</td>
<td>Complex Task III (using a To-Do List)</td>
<td></td>
</tr>
<tr>
<td>&quot;STOP!&quot; → Present-mindedness (Breath Focus) → Check mental blackboard → (Re)State your goal → Split the task into subtasks</td>
<td>Complex Task III (using a To-Do List)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. Checking</th>
<th>Complex Task III (using a To-Do List)</th>
<th>GMT review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumstances can change, and everyone makes mistakes</td>
<td>Complex Task III (using a To-Do List)</td>
<td></td>
</tr>
<tr>
<td>So: make it a habit to STOP! and CHECK!</td>
<td>Complex Task III (using a To-Do List)</td>
<td></td>
</tr>
</tbody>
</table>

| GMT review | Complex Task III (using a To-Do List) | GMT review |
Figure 1. Illustration of GMT strategy cycle

STOP!

Focus attention in the present

STATE your goal

SPLIT a complex task into subtasks

CHECK!

“What am I doing?”

“What is my main goal?”

“Is this going to help?”

(Policeman illustration by Tom Manly, Used with permission.)
### Table 4. Outline of Brain Health Workshop (BHW) sessions

<table>
<thead>
<tr>
<th>Session</th>
<th>Key Concepts</th>
<th>Within-Session Exercises</th>
<th>Between-Session Assignments</th>
</tr>
</thead>
</table>
| 1. Introduction to Brain Health | Introductions  
Basic brain anatomy  
Basic brain functions ("knowledge zones")  
Effects of MS and objectives of BHW | Warm-up / Introductions exercise  
Making a brain map  
Identifying knowledge zones required for brain "challenges"  
Review and discussion of material in relation to participants' personal experiences | Reading: Brain facts  
Daily brain "challenges" (e.g., word-finding, word games, puzzles, mazes) |
| 2. Brain Function and MS | What is MS and how can it affect the brain?  
How we look at the brain and brain function  
Brain changes and adaptation in MS | Review and discussion (homework, new material, personal experiences) | Readings: Causes and effects of MS  
Daily brain challenges |
| 3. Neuroplasticity | Brain review: Neurons and synapses  
Mind Sculpture: Basic principles of neuroplasticity  
The "Mental Gym" and "Hebb's rule"  
Adaptation to brain injury: Restoration and compensation | Review and discussion (homework, new material, personal experiences)  
Working out in the "mental gym": timed mazes | Readings: Neuroplasticity  
Daily brain challenges |
| Individual appointment with Trainer to discuss program progress | | Brain Jeopardy (review) | |
| 4. Memory | Types of memory  
Memory processes  
Memory and the brain  
Sources and types of memory problems  
Normal forgetting vs. memory problems | Review and discussion (homework, new material, personal experiences)  
Encoding (with delayed recognition) exercise: Word list  
Demonstration of "false memory effect": Word list | Readings: Memory  
Daily brain challenges  
Self-assessment: visual or verbal learning style |
| 5. Attention and Problem-Solving | The many facets of attention  
Attention and the brain  
Sources and types of attention problems  
The "inner CEO" and problem-solving  
Problem-solving, the brain and MS  
Creativity | Review and discussion (homework, new material, personal experiences)  
Demonstration of selective attention (the "Stroop effect") | Readings: Attention: Problem-Solving with MS  
Daily brain challenges |
### 6. Vision, Movement and Language

- The visual system; vision and MS
- The motor system
- Motor aspects of MS, assistive devices
- Language and the brain; verbal skills and MS

- Demonstration of the visual system at work (optical illusions)
- Review and discussion (homework, new material, personal experiences)

- Readings: Vision, movement and language
- Daily brain challenges

---

**Individual appointment with Trainer to discuss program progress**

### 7. Lifestyle I: Diet and Physical Fitness

- Nutrition and the brain
  - Nutritional guidelines: Canada's Food Guide
  - Brain benefits of physical exercise
  - Physical exercise and MS

- Review and discussion (homework, new material, personal experiences)

- Readings: MS and nutrition; Exercising with MS
  - Plan a day's worth of meals and snacks based on the reading and Canada Food Guide
  - Log: Keep a nutrition diary for one week

### 8. Lifestyle II: Sleep and the Brain

- Sleep, brain function and brain health
- Sleep, fatigue and MS
- Sleep hygiene and energy conservation

- Review and discussion (homework, new material, personal experiences)
- Epworth Sleepiness Scale

- Readings: Sleep and the brain
  - Log: Keep a sleep diary for one week
  - Daily brain challenges

### 9. Lifestyle III: Stress and the Brain

- What is Stress?
- How stress can influence body and brain function
- "Good" vs "bad" stress
- Stress management
- BHW review

- Review and discussion (homework, new material, personal experiences)

- Brain Jeopardy (review)
3.3 Data analysis

3.3.1 Neuropsychological measures

3.3.1.1 Preparation of neuropsychological data

Behavioural data (from baseline, post-training and 6-month follow-up assessments) were inspected for outliers and distribution. Extreme outliers at the lower and upper tails were winsorized to the 1st and 99th percentile respectively.

Following this, all baseline behavioural data approximated normal distributions with the exception of the following measures: errors on the SDMT (both Oral and Written versions), errors on the Trail-Making Test (both A and B) and errors on FAS. These variables were positively skewed, as defined by skewness > twice the standard error of skewness. In addition, the Hotel Task Garage Deviation Score is an ordinal variable, and was negatively skewed. Group differences on these variables were therefore analyzed with the non-parametric Mann-Whitney U test. MS patients’ post-training and 6-month follow-up data also approximated normal distributions (skewness < twice the standard error of skewness) with the exception of Tower Test rule violations, whose distributions were positively skewed as patients reached ceiling on subsequent test sessions. Performance changes on this variable and the Hotel Task garage deviation score were analyzed with the non-parametric Wilcoxon signed-rank test.

Performance on the TEA subtest 2 was at ceiling for the vast majority of all participants at all test sessions, and these data were not further analyzed for group or time effects.

3.3.1.2 Design of neuropsychological analyses

3.3.1.2.1 Characterizing executive dysfunction in MS

Standard parametric (t-test) and non-parametric (Mann-Whitney U test) univariate analyses were used to compare baseline performance of the MS patient and neurologically healthy control groups. In light of the unequal numbers of MS patients (n = 29) and controls (n = 10), particular attention was paid to examining equality of variance between these groups. Where Levene’s Test for equality of variances was significant (p < .05) and the variance in one group was > twice the variance in the comparison group, Welch’s t-test statistics are reported in lieu of Student’s t-tests.
An alpha level of $p < .05$ was used for all tests. Given the use of a multi-level assessment battery to assess multiple processes at different levels of ecological validity (Stubberud, et al., 2013) and test the a priori hypotheses concerning the extent of executive deficits in MS, adjustments were not made for multiple comparisons (Perneger, 1998).

Relations among behavioural indices of the SART were analyzed using Pearson correlations. The multivariate method of partial least squares (PLS) was used to explore relations across larger data subsets, e.g. between cognitive test scores, self- and informant-rated executive dysfunction and quality of life indicators (self-rated mood and sleep quality). For these analyses, a subset of the twenty-two cognitive-behavioural test scores that approximated normal distributions and were most pertinent to executive control (plus an estimate of general cognitive ability) were selected (Table 5). These were reverse-coded as needed to facilitate interpretation, with positive values indicating better performance on all variables.

Briefly, in PLS the cross-block correlation matrix between two sets of variables is decomposed (using singular value decomposition) into one or several orthogonal latent variables (LVs) each optimized to describe a dimension of the relationship between the variable sets (Krishnan, Williams, McIntosh, & Abdi, 2011; McIntosh & Lobaugh, 2004). Two types of PLS were used in the current study: mean-centered and behavioural. Mean-centered PLS was used to analyze group differences (e.g., MS patients and controls) in sets of dependent variables (e.g., mean amplitudes in the ERP components and regions of interest). Behavioural PLS was used (within or between groups, as described for each analysis) to determine the relationship between sets of predictor variables (e.g. mean ERP amplitudes) and dependent variables (e.g., cognitive test scores). In both types of PLS the statistical significance of each LV was determined by comparing the probability of its associated singular value to values derived from 500 random permutations; significance was set at $p < .05$. With the multivariate analysis of all variables simultaneously, correction for multiple comparisons is unnecessary (Friston, et al., 1995). The reliability with which each predictor variable in the dataset contributed to the obtained LV(s) was determined through 500-permutation bootstrap resampling followed by calculation of bootstrap ratios ($BSR = \text{salience divided by the standard error from resampling}$). For interpretive purposes, BSRs are somewhat analogous to $z$ scores (McIntosh & Lobaugh, 2004); a BSR of 2 or greater exceeds the 95% confidence interval and was used as the “significance” threshold in these analyses (Efron & Tibshirani, 1985).
Table 5. Multivariate subsets of cognitive test variables used in analyses

<table>
<thead>
<tr>
<th>Test</th>
<th>Component process(es) ‡</th>
<th>Variable included at Baseline</th>
<th>Variable included at Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASAT 3&quot; (total correct)</td>
<td>Processing speed, attention (sustained, switching), working memory</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PASAT 2&quot; (total correct)</td>
<td>Processing speed, attention (sustained, switching), working memory *</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Digit Span, forward (total)</td>
<td>Attention span</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Digit Span, backward (total)</td>
<td>Working memory</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Shipley (SILS Vocabulary)</td>
<td>Estimated general intellectual ability</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>SDMT, oral (total correct)</td>
<td>Processing speed, visual scanning</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>SDMT, written (total correct)</td>
<td>Psychomotor speed, visual scanning</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Trail Making Test, total errors</td>
<td>Attention (sustained, selective)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Trail Making Test, Time B – Time A</td>
<td>Attention (switching)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>FAS (total correct)</td>
<td>Verbal fluency (strategic semantic retrieval), attention (switching) **</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>SART, commission errors (%)</td>
<td>Attention (sustained), inhibitory control</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>SART, omission errors (%)</td>
<td>Attention (sustained)</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>SART, cvRT (msec)</td>
<td>Attention (sustained)</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>SART, PES (msec)</td>
<td>Attention (sustained), error monitoring and adaptive self-correction</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>TEA-3: Elevator Counting with Distraction (auditory)</td>
<td>Attention (sustained, selective)</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>TEA-4: Elevator Counting with Reversal (visual)</td>
<td>Attention (switching)</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>TEA-5: Elevator Counting with Reversal (auditory)</td>
<td>Attention (sustained, switching), working memory</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Tower, achievement score</td>
<td>Planning, working memory (sequencing)</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Tower, move-accuracy ratio</td>
<td>Planning, working memory (sequencing)</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Tower, rule violations (total)</td>
<td>Self-monitoring, attention to task rules</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hotel, number of tasks attempted</td>
<td>Self-monitoring, attention to task goal</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Hotel, deviation from optimal time on task (msec)</td>
<td>Self-monitoring, attention to task goal</td>
<td>22</td>
<td>11</td>
</tr>
</tbody>
</table>

‡ As described in test administration and reference material and/or neuropsychological compendiums (Lezak, et al., 2004; Strauss, et al., 2006)

* Greater cognitive load relative to PASAT 3" owing to the more rapid rate of stimulus presentation (Strauss, et al., 2006)

** Word retrieval to phonemic cues has been shown to depend on the participant’s ability to organize retrieval by clustering and especially to switch between subcategories (Troyer, Moscovitch, & Winocur, 1997)
3.3.1.2.2 Evaluating rehabilitation outcome

MS patients’ change on the neuropsychological outcome measures was evaluated using 2 x 3 mixed design ANOVAs with Treatment (GMT, BHW) as the between-subjects factor and Time (baseline, post-training, 6-month follow-up) as the within-subjects factor. Sphericity was examined and the Greenhouse-Geisser correction applied as needed. Main effects of Time were clarified with post hoc Bonferroni-corrected contrasts. The partial eta squared ($\eta_p^2$) statistic was used to interpret the strength of omnibus effects. Where indicated to test the a priori hypotheses of improved cognitive and functional test performance and informant-rated executive functioning in daily activities, main effects of Time and Treatment by Time interaction effects were clarified with a calculation of effect sizes (Cohen’s d) and paired t-tests describing differences in performance by test time (baseline to post-training, or baseline to follow-up) within each intervention group (Stubberud, et al., 2013). An alpha level of $p < .05$ was used for all planned contrasts. Corrections for multiple comparisons were avoided to preserve statistical power to detect multi-level treatment effects according to the a priori hypotheses (Perneger, 1998).

Owing to violations in assumptions for the use of ANOVAs (specifically the use of an ordinal variable and/or a non-normal data distribution), intervention-related changes on the Hotel Test (garage deviation score), Tower Test (rule violations) and GAS were analyzed using Wilcoxon signed-ranks tests within each intervention group. Groups were also compared on their degree of GAS change using the Mann-Whitney U test.

3.3.1.2.3 Composite scores

In addition to analyses of intervention-related change on the individual outcome variables, composite scores were calculated to provide an overall and more reliable index of change in each of four broad domains: (a) objective, standardized tests of attention and executive functioning (using the set of 11 outcome measures listed in Table 5); (b) patients’ self-rated “real-life” executive functioning (combining CFQ total score and DEX subscores); (c) informant ratings of patients’ executive functioning (combining subscore totals from the DEX “other” rating form); and (d) patients’ self-rated quality of life in terms of mood (POMS subscores) and sleep quality (PSQI global score). For each of the outcome measures listed in Table 5, patients’ total and/or subtest scores at baseline, post-training and 6-month follow-up were converted to z-scores using...
the baseline mean for each variable for the overall MS patient group. For ease of interpretation, all z-scores were calculated such that positive values corresponded to better performance relative to the group mean at baseline (i.e., for some tests, this referred to a lower score). Paired t-tests were used to compare post-training and follow-up group mean composite scores within the GMT and BHW groups.

3.3.1.2.4 Composite change scores

Composite change scores were also calculated for each of the above four domains (standardized executive / attention tests, self-rated everyday executive functioning, informant ratings of patients’ executive functioning, and self-rated quality of life). These were calculated separately for baseline-to-post-training and baseline-to-follow-up change by subtracting each patient’s composite scores at baseline from their associated composite scores at post-training or follow-up, respectively. Positive values indicated improvement on the outcome measure relative to that patient’s baseline. Group differences in the extent of change at post-training and follow-up were analyzed using t-tests. Further, within-group relations of these composite change scores to baseline disease severity (disease duration, neurological severity ratings)\(^4\) and mood disturbance were tested using behavioural PLS to explore variability in patients’ response to intervention.

3.3.2 Neurophysiological measures

3.3.2.1 Preparation of EEG data

All analyses were conducted in EEGLAB (Delorme & Makeig, 2004) and ERPLAB (http://www.erpinfo.org/erplab). High- and low-pass filter half-amplitude cut-offs were conservatively set at 0.1 and 80 Hz, respectively. An average reference was computed offline and used for all analyses. Trials contaminated by excessive artifacts were rejected automatically before averaging with a step function (Luck, 2005) with a voltage threshold of ± 100 μV in moving windows of 200 ms and with a window step of 100 ms.

\(^4\) These measures were used as an estimate of the extent of DWMI in the sampled MS patients. Structural MRI scans were included in the assessment protocol with the aim of obtaining a more direct measure of regional and whole-brain white matter atrophy (Dade, et al., 2004), however several patients were unable to complete these scans. Of particular note, no facilities were available to assist patients with mobility impairments who were unable to transfer independently onto the scanner bed. This resulted in a biasing of the sample of scanned patients toward those with less progressed disease. The available MRI data will be analyzed and reported separately from this dissertation.
The continuous EEG data were segmented into epochs of 1.2 seconds (-400 to 800 ms after stimulus onset). Time windows for stimulus-locked ERPs were computed with a mid-peak latency technique, also referred to as the fractional latency approach (Picton, Bentin, et al., 2000). For example, peak latency of the P2 component for No-go trials was measured from the grand average at the Cz electrode. Latencies of the preceding and following peaks (here, the N2 and P3 respectively) were each added to that of the P2, and the resulting sums divided by 2 to obtain the onset and offset of the P2 component. With MS causing delayed ERP latencies even early in the disease process (Aminoff & Goodin, 2001; Honig, et al., 1992; Leocani & Comi, 2000; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Bramham, et al., 2010), determination of ERP windows was done separately for patients and controls. For controls, the time windows obtained were: 110-160 ms post-stimulus onset for the N1, 160-260 for the P2, 260-360 for the N2 and 390-590 for the P3. For MS patients, the time windows obtained were: 115-185 for the N1, 185-275 for the P2, 275-375 for the N2 and 430-630 for the P3. Of these stimulus-linked ERPs, only the P3 data were analyzed and reported for this dissertation. Inspection of the response-locked ERN and Pe waveforms showed no latency differences between controls and MS patients. Time windows for analysis of these components’ mean amplitudes were defined in accordance with prior research and used for all participants: 0-100 ms post-response for the ERN and 200-400 ms post-response for the Pe (Larson, Baldwin, Good, & Fair, 2010; Nieuwenhuis, et al., 2001; Olvet & Hajcak, 2009; Pontifex, et al., 2010). Mean ERP amplitudes were measured relative to the mean amplitude taken over a 200 ms pre-stimulus baseline for the stimulus-locked P3 and a 400-to-200 ms pre-response baseline for the response-locked ERN and Pe.

3.3.2.2 Analysis of ERP data

Analyses were carried out on frontal and parietal regions of interest (ROIs) based on the topographical distributions of the components under study (e.g., as reviewed in Chapter 1). For each subject, mean amplitudes in the relevant time window for each component of interest were averaged across the electrodes within each ROI. For the P3, six ROIs were defined: fronto-central, right and left frontal, centro-parietal and left and right parietal (Figure 2a). For the error-response-linked components, a fronto-central ROI was created for the ERN and a centro-parietal ROI was created for the Pe (Figure 2b). This ROI approach was taken to facilitate comparison of results with those from prior research employing similar ERP analytic methodology. (Whole-
brain PLS analyses of ERP data as well as other EEG indices will be carried out and reported separately from this dissertation.)

SART trial types of interest for the P3 included correct Go and No-go (“Stop”) trials, incorrect Go and No-go trials (omission errors and commission errors, respectively) and amplitudes averaged from the three Go trials preceding and following No-go Stops and Errors (i.e., pre-Stop, post-Stop, pre-Error and post-Error). Mean amplitudes for the error-related ERP components (ERN and Pe) were calculated by subtracting the amplitudes of the response-locked waveforms on correct Go trials from those on incorrect No-go trials. This provided an estimate of error-related activity specific to the No-go error trials, corrected for any activity associated with the motor response (which was also made on correct Go trials) according to standard procedure for ERN/Pe analyses (e.g., Falkenstein, et al., 1991; Herrmann, et al., 2004; Yeung, et al., 2004).

**Figure 2. Regions-of-interest electrode groupings**

(a) P3 frontal (orange) and parietal (green)  
(b) ERN (red) and Pe (blue)
3.3.2.2.1 Characterizing baseline neurocognitive function in MS

Standard univariate analyses were used to explore ERPs in relation to task demand (SART trial type) and response accuracy in the control and MS patient groups. As described with the results in Chapter 4, repeated-measures ANOVAs to analyze mean P3 amplitude effects included trial type (e.g., Go, No-go) and/or accuracy (correct, error) and ROI (fronto-central, left and right frontal, centro-parietal, left and right parietal) as within-subjects factors. The alpha level was set to $p < .05$. Specific contrasts were used to test the series of a priori hypotheses and corrections for multiple comparisons (between the ANOVAs) were not made (Perneger, 1998). Error-processing activity (i.e., ERN and Pe) was quantified with t-tests comparing mean amplitudes of No-go error to correct Go trials to isolate error-processing activity (Falkenstein, et al., 1991; Herrmann, et al., 2004; Yeung, et al., 2004).

Mean-centered PLS was used to compare ERP amplitudes in the relevant ROIs between control and patient groups. As with the analysis of behavioural measures within the MS patient group, behavioural PLS was used to investigate correlations between mean amplitudes in the components of interest (P3, ERN, Pe) and indices of disease progression (disease duration, neurological disability ratings) with the latter entered as the “behaviour” variables.

3.3.2.2.2 Evaluating rehabilitation outcome

As with the neuropsychological indices, 2 x 3 mixed design ANOVAs with Treatment (GMT, BHW) as the between-subjects factor and Time (baseline, post-training, 6-month follow-up) as the within-subjects factor were used to assess group changes in mean amplitudes for the ERP components of interest (P3, ERN, Pe). Analysis of change in mean P3 amplitudes had the additional within-subjects factor of ROI (fronto-central, right and left frontal, centro-parietal and left and right parietal). Analyses of change in mean amplitudes of the response-related components (ERN and Pe) were done in the relevant fronto-central ROI for the ERN and centro-parietal ROI for the Pe.
3.3.3  Relating neuropsychological and neurophysiological functioning

3.3.3.1  ERP amplitudes in relation to executive-attentive behaviour in neurologically healthy controls and MS patients at baseline

Behavioural PLS was used to assess the relation between ERPs and behavioural performance. Two sets of PLS analyses were done, the first specific to behavioural indices in the EEG task (SART) itself, the second to explore whether any such identified neurocognitive pattern generalized more broadly to participant performance across the subset of executive-attentional tests (Table 5) that were completed “offline” (i.e., not during the EEG recording). Effects in the control and patient groups were assessed simultaneously.

For the ERP variables, mean amplitudes of interest for the P3 included correct Go SART trials (that provide an index of tonic sustained attention over the majority of task trials), correct No-go trials (that demand additional attention and response control) and pre-to-post-Error amplitude change (hypothesized to reflect attentional up-regulation in conjunction with performance monitoring). Mean amplitudes for the ERN and Pe (No-go errors – correct Go trials) were interpreted as indices of response conflict and performance monitoring.

3.3.3.2  Relation of ERP change to behavioural change post-intervention

Behavioural PLS was also used to explore the relation of change in mean ERP amplitudes to behavioural change as a function of treatment (GMT, BHW). These included SART behavioural variables (i.e., performance within the EEG task itself) and the other outcome measures of executive-attentional functioning completed “offline” (Table 5). Analyses were done separately for post-training and the 6-month follow-up but included all ERPs of interest (P3, ERN and Pe).

3.4  Procedure

3.4.1  Participant recruitment

Participating MS patients were recruited through MS clinics at Baycrest Centre for Geriatric Care (Baycrest) and Sunnybrook Health Sciences Centre (SHSC). Baycrest’s MS clinic operates through the Assistive Technology Clinic. Recruitment pipelines varied somewhat by institution, in accordance with their ethics review board and as supervised by the director of each MS clinic.
These directors and their nominated associates served as clinical collaborators for this research program (refer to the Acknowledgments).

At Baycrest, a consulting neurologist at the Elkie Adler MS Clinic identified potential participants through brief cognitive testing and clinical presentation. These candidates were then contacted by an MS Clinic occupational therapist to introduce the study and confirm the patient’s interest and ability to participate before obtaining verbal consent for referral to the Levine lab research assistant (LLRA) designated as the participant coordinator for the study. At SHSC, two recruitment paths were used. First, pamphlets describing the study to potential participants were placed in the MS Clinic for visiting patients to learn about the study and independently contact the LLRA for further information or to participate. Second, to reach patients not visiting the clinic during the recruitment period, staff at the SHSC MS Clinic in conjunction with the SHSC Neuropsychiatry Program (to which the MS Clinic refers patients for cognitive testing) identified potential subjects based on clinical presentation and relevant chart data and, as with Baycrest, provided the initial contact to introduce the study and confirm the patient’s interest and ability to participate before referral to the LLRA.

The LLRA contacted referred patients by telephone to explain and answer any questions about the study activities and requirements and conduct a screening interview to confirm eligibility according to the inclusion/exclusion criteria (Section 3.1). Verbal consent to participate was obtained during this telephone call. Written consent was obtained at the participant’s first appointment for assessment at Baycrest. All study activities – all testing sessions, training sessions, and individual appointments to discuss the patient’s progress and any concerns during the study – took place at the Rotman Research Institute at Baycrest. Patients were assured verbally and in writing that participation was voluntary at all times and would have no impact on access to regular services at Baycrest and/or SHSC (as applicable). A total of 29 MS patients were thus sequentially enrolled into Study 1 (characterization of executive dysfunction in MS). Once a sufficient number had agreed to form intervention groups (n = 4-5) to continue into the rehabilitation arm of the study, patients were randomly assigned to one of the two programs (GMT, BHW) and a 9-week trial began. Enrolment continued until three groups of patients had completed each of the interventions (n = 14 in each intervention group).
Neurologically healthy control participants were recruited from the Rotman Research Institute’s Subject Database (at Baycrest) via telephone or email contact by the LLRA per the policies regulating this participant pool. A total of 10 participants were tested, matched to the sample of 29 MS patients on age, sex, and education variables. Explanation of the study, screening for inclusion/exclusion criteria, and obtaining of verbal consent was done via telephone by the LLRA with written consent obtained at the participant’s assessment appointment at Baycrest.

3.4.2 Baseline assessment

MS patients’ initial (i.e., baseline) assessment required approximately 7 hours and was done over two separate appointments to minimize the risk and impact of fatigue. At the first appointment, the LLRA obtained written informed consent, ensuring the participant understood the nature of all study activities, design (e.g., two parts to the study: baseline and rehabilitation) and requirements including inclusion criteria and time commitment. The baseline set of neuropsychological tests and questionnaires was administered (Table 1) and participants were given a DEX rating form to be completed by their informant (a close or significant other) of choice and returned in a sealed pre-paid envelope. EEG recording was done in a second appointment with tasks as outlined above in Section 3.2.2. Rest breaks were built into the protocol and extended as needed to minimize patient fatigue. When feasible, participants also completed a structural MRI scanning session (data not included in this dissertation).

All assessments were conducted by a research assistant blind to the patients’ intervention group assignment and to expected study outcomes. The research coordinator (i.e., author of this dissertation) viewed patients’ test results (e.g., to determine eligibility for the rehabilitation trial) coded with participant ID numbers only, in order to remain blind to the performance of patients who subsequently participated in the intervention groups that were led by the author.

Neurologically healthy controls completed the same set of neuropsychological measures as the MS patients at baseline, with the exception of goal attainment scaling (Table 1). Controls also completed the EEG recording session as described in Section 3.2.2.

3.4.3 Rehabilitation trial

MS patients participating in the rehabilitation study arm (28 of 29 patients who completed baseline assessment) were randomly assigned to treatment (GMT) and control (BHW) programs
in groups of 4-5. Previous experiences with the GMT and BHW programs in other populations had suggested 4-5 as an optimal group size to balance individual attention with opportunity for discussion and peer support. With the sequential enrolment design, participants’ baseline assessments were conducted within 2 months prior to starting their intervention program.

Each patient in the GMT and BHW programs attended weekly 2-hour sessions over the course of nine weeks. Sessions were led by the author with support from an additional trainer (these were an occupational therapist experienced in working with MS patients or a post-doctoral fellow completing supervised psychological practice hours). None of the trainers were involved at any time with participant assessment.

Both GMT and BHW programs were administered in highly interactive, client-centered and experience-oriented didactic group sessions, with specific content and activities as outlined in Section 3.2.3 and Tables 3-4. Participants in the GMT group applied the strategies learned to an individual project that was one of two goals for which they had completed goal attainment scaling during the baseline assessment (Section 3.2.1). Each GMT patient’s other identified goal was not discussed until the post-training assessment. As noted earlier, BHW participants also identified two goals through GAS during baseline assessment, but were not guided to actively work on these during training.

Participants who missed a scheduled group session completed an individual make-up session by the trainer prior to the next scheduled group module. Attendance rates for the GMT and BHW group sessions are provided in Chapter 5. Whether in the group or including individual sessions, all study participants completed all assigned training sessions.

Participants in both GMT and BHW groups were also provided two private 30-minute appointments with the author (scheduled after the third and sixth training sessions, as outlined in Tables 3-4) to discuss their progress and any concerns or questions about program content, activities and assignments.

3.4.4 Evaluation of rehabilitation outcome

Following completion of their assigned intervention program, participating MS patients completed the post-training outcome assessment battery. This included repeat assessment (with alternate forms, where available) on a subset of the cognitive, functional-behavioural, and self-
report measures administered at baseline (see Tables 1 and 5) and a second EEG recording session, identical to the paradigm at baseline. Total post-training test time was approximately 5 hours, again typically done in two sessions (one for neuropsychological testing and one for EEG) to minimize the risk and impact of fatigue. With the number of patients and testing sessions involved, testing was carried out over 6 weeks post-training. A new copy of the DEX rating form was sent to each participant’s informant, who was blinded as to which intervention the patient had completed, for return in a sealed pre-paid envelope.

Six months following completion of their intervention program and post-testing, patients completed a final 5-hour follow-up assessment, identical to the post-training assessment, to evaluate longer-term rehabilitation outcomes for the GMT and BHW programs.
Chapter 4
Results: Executive dysfunction in MS

4.1 Effects of MS on neuropsychological measures

4.1.1 Comparison of MS patients and controls

Demographic data for the total sample of MS patients and controls are summarized in Table 6. MS patients and controls were well-matched for age, \( t(37) = .985 \) (\( p > .3 \)), and education, \( t(37) = .137 \) (\( p > .8 \)). Groups were less well matched for sex, with a marginally greater female-to-male ratio in the MS group, \( \chi^2 = 3.155, p = .076 \). With respect to disease characteristics, the MS group contained a roughly equal number of relapsing-remitting and secondary progressive patients (also see Section 4.1.2 and Table 10). Median EDSS was 3.5, with individual scores ranging from 1 to 8 (i.e. close to the full available EDSS range of 1 to 9.5, see Kurtzke, 1983).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (years)</th>
<th>Education (years)</th>
<th>F : M</th>
<th>RR : Prog</th>
<th>EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Median</td>
</tr>
<tr>
<td>MS patients</td>
<td>29</td>
<td>51.8</td>
<td>10.5</td>
<td>16.1</td>
<td>2.7</td>
<td>23 : 6</td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
<td>47.4</td>
<td>16.5</td>
<td>16.0</td>
<td>2.9</td>
<td>5 : 5</td>
</tr>
</tbody>
</table>

Group results on cognitive test scores are summarized in Table 7. MS patients showed no impairment relative to controls in estimated intelligence, verbal fluency or visual-spatial perception (p’s > .1).

As a group, MS patients were consistently impaired on indicators of information processing and psychomotor speed, including Trails A, \( t(36.8) = 4.310, p < .001 \), Trails B, \( t(35.9) = 3.362, p = .002 \), and both written, \( t(37) = 3.348, p = .002 \), and oral, \( t(37) = 2.619, p = .013 \), versions of the SDMT. (Groups did not differ significantly in SDMT errors, p > .3.) Mean SART reaction time (RT), \( t(36.0) = 2.370, p = .023 \), and post-error slowing (PES), \( t(34.2) = 2.341, p = .025 \), were also greater for MS patients. RT variability (cvRT) did not significantly differ between groups.
Table 7. Summary of cognitive test performance in MS patients and controls

<table>
<thead>
<tr>
<th></th>
<th>MS patients</th>
<th></th>
<th>Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean</td>
<td>SD</td>
<td>Median</td>
</tr>
<tr>
<td>Shipley</td>
<td>32.0</td>
<td>31.3</td>
<td>7.3</td>
<td>37.5</td>
</tr>
<tr>
<td>FAS (total correct)</td>
<td>37.0</td>
<td>34.9</td>
<td>11.3</td>
<td>35.5</td>
</tr>
<tr>
<td>JLO</td>
<td>23.0</td>
<td>23.3</td>
<td>5.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Trails A (time)</td>
<td>45.0</td>
<td>49.0</td>
<td>19.6</td>
<td>31.0</td>
</tr>
<tr>
<td>Trails B – A (time)</td>
<td>57.0</td>
<td>81.5</td>
<td>57.3</td>
<td>39.5</td>
</tr>
<tr>
<td>Trails A + B (errors)</td>
<td>1.0</td>
<td>0.8</td>
<td>0.9</td>
<td>0.0</td>
</tr>
<tr>
<td>SDMT Oral (total correct)</td>
<td>41.0</td>
<td>43.2</td>
<td>14.9</td>
<td>56.5</td>
</tr>
<tr>
<td>SDMT Written (total correct)</td>
<td>35.0</td>
<td>35.9</td>
<td>12.9</td>
<td>50.0</td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>9.5</td>
<td>9.6</td>
<td>2.3</td>
<td>9.0</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>7.0</td>
<td>6.8</td>
<td>2.2</td>
<td>5.0</td>
</tr>
<tr>
<td>PASAT 3&quot;</td>
<td>36.0</td>
<td>36.2</td>
<td>12.1</td>
<td>41.0</td>
</tr>
<tr>
<td>PASAT 2&quot;</td>
<td>30.0</td>
<td>28.9</td>
<td>9.9</td>
<td>31.5</td>
</tr>
<tr>
<td>TEA 3</td>
<td>6.0</td>
<td>6.1</td>
<td>3.2</td>
<td>8.0</td>
</tr>
<tr>
<td>TEA 4</td>
<td>7.0</td>
<td>7.1</td>
<td>2.0</td>
<td>9.0</td>
</tr>
<tr>
<td>TEA 5</td>
<td>4.0</td>
<td>4.2</td>
<td>2.9</td>
<td>4.0</td>
</tr>
<tr>
<td>SART Commission Errors</td>
<td>30.4</td>
<td>39.7</td>
<td>21.8</td>
<td>34.4</td>
</tr>
<tr>
<td>SART Omission Errors</td>
<td>2.4</td>
<td>4.9</td>
<td>4.9</td>
<td>1.5</td>
</tr>
<tr>
<td>SART Mean RT</td>
<td>437.2</td>
<td>439.3</td>
<td>95.8</td>
<td>369.3</td>
</tr>
<tr>
<td>SART cv RT</td>
<td>0.3</td>
<td>0.3</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>SART Post-Error Slowing</td>
<td>18.7</td>
<td>46.6</td>
<td>80.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Hotel # Tasks Attempted</td>
<td>5.0</td>
<td>4.2</td>
<td>1.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Hotel Time Deviation (sec)</td>
<td>486.0</td>
<td>493.0</td>
<td>273.3</td>
<td>423.5</td>
</tr>
<tr>
<td>Hotel Garage Deviation Score</td>
<td>7.0</td>
<td>6.1</td>
<td>2.6</td>
<td>8.0</td>
</tr>
<tr>
<td>Tower Achievement Score</td>
<td>7.0</td>
<td>7.1</td>
<td>3.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Tower Move Accuracy Ratio</td>
<td>1.4</td>
<td>1.4</td>
<td>0.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Tower Rule Violations</td>
<td>2.0</td>
<td>2.1</td>
<td>1.3</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Boxed values indicate differences significant at p < .05.
Shaded boxed values indicate marginally significant (.05 < p < .10) differences.
* Mann-Whitney U test in lieu of Student’s t-test.
MS patients were impaired on tests requiring the executive capacity for attentional switching, including the difference in time to complete Trails B over Trails A, $t(32.7) = 2.431$, $p = .021$, and scores on the Visual Elevator subtest of the TEA, $t(37) = 2.237$, $p = .031$.

Executive deficits were also apparent as neglect of task goals or rules for task completion. MS patients committed a greater number of rule violations on the Tower Test, $t(37) = 2.879$, $p = .007$. On Trails A and/or B, 55.2% of MS patients compared to 30% of controls committed at least one error, however (as with errors on the SDMT and FAS) the between-group comparison on Trails errors did not reach significance ($p > .1$). On the Hotel Task, patients attempted significantly fewer tasks, $t(34.0) = 2.103$, $p = .043$, and were less able to prospectively remember to open the garage doors at the instructed times, resulting in marginally lower Garage Deviation scores, $U = 93.5$, $p = .073$.

Performance on both the 3” and 2” versions of the PASAT did not differ significantly between groups ($p$’s > .2), nor did scores on the forward Digit Span ($p > .4$). Patients marginally outperformed controls on the backward Digit Span, $t(36) = -1.932$, $p = .061$.

Group results on the questionnaires assessing perceived cognitive functioning are shown in Table 8. MS patients reported significantly greater deficits compared to controls on the CFQ, $t(37) = 2.856$, $p = .007$, and on the Intention ($t(37) = 3.285$, $p = .002$) and Executive Memory ($t(37) = 2.636$, $p = .012$) subscales of the DEX (as well as DEX Total scores, $t(37) = 3.285$, $p = .002$). Patients also reported marginally higher deficits in Inhibition ($t(37) = 1.748$, $p = .089$) and Positive Affect ($t(37) = 1.953$, $p = .058$) on the DEX.

Two patient informants and one control informant failed to return the DEX “other” rating scales. For the remaining participants, informant ratings were higher for patients on the Inhibition ($t(33) = 3.510$, $p = .001$), Intention ($t(34) = 2.506$, $p = .017$), Executive Memory ($t(34) = 3.399$, $p = .002$) and Positive Affect ($t(32.7) = 3.371$, $p = .002$) subscales of the DEX (as well as Total scores, $t(34) = 2.532$, $p = .016$). Self and informant ratings on the Negative Affect DEX subscale did not differ between groups (both $p$’s > .3). The discrepancy between total informant ratings and self-ratings was minimal in both patient and control groups with no between-group difference ($p > .6$).
Table 8. Summary of self- and informant-rated everyday executive functioning in MS patients and controls

<table>
<thead>
<tr>
<th></th>
<th>MS patients</th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean</td>
<td>SD</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>CFQ</td>
<td>44.0</td>
<td>45.4</td>
<td>15.7</td>
<td>32.5</td>
<td>30.1</td>
</tr>
<tr>
<td>DEX (Self ratings)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>8.0</td>
<td>8.3</td>
<td>4.9</td>
<td>4.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Intention</td>
<td>8.0</td>
<td>7.6</td>
<td>3.7</td>
<td>3.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Executive Memory</td>
<td>2.0</td>
<td>2.7</td>
<td>1.9</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Positive Affect</td>
<td>3.0</td>
<td>3.7</td>
<td>2.4</td>
<td>1.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>2.0</td>
<td>2.3</td>
<td>1.6</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Total</td>
<td>24.0</td>
<td>25.0</td>
<td>12.8</td>
<td>11.0</td>
<td>13.1</td>
</tr>
<tr>
<td>DEX (Other ratings)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>7.0</td>
<td>8.5</td>
<td>6.7</td>
<td>3.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Intention</td>
<td>7.0</td>
<td>7.8</td>
<td>5.1</td>
<td>1.0</td>
<td>3.1</td>
</tr>
<tr>
<td>Executive Memory</td>
<td>3.0</td>
<td>3.1</td>
<td>2.8</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Positive Affect</td>
<td>3.0</td>
<td>4.1</td>
<td>3.5</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Negative Affect</td>
<td>2.0</td>
<td>1.9</td>
<td>1.5</td>
<td>1.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Total</td>
<td>22.0</td>
<td>25.6</td>
<td>17.6</td>
<td>6.0</td>
<td>9.9</td>
</tr>
<tr>
<td>DEX Total (Other - Self)</td>
<td>0.0</td>
<td>-0.6</td>
<td>13.6</td>
<td>-6.0</td>
<td>-2.9</td>
</tr>
</tbody>
</table>

Boxed values indicate differences significant at p < .05.
Shaded boxed values indicate marginally significant (.05 < p < .10) differences.

Group results on the self-report measures of mood and sleep quality are shown in Table 9. One patient and one control failed to complete the POMS. Compared to controls, MS patients as a group reported greater levels of overall mood disturbance on the POMS, t(35) = 2.820, p = .008, with significantly greater endorsement of items on the Tension-Anxiety (t(35) = 2.991, p = .005), Dejection-Depression (t(35) = 2.716, p = .010) and Confusion-Bewilderment (t(35) = 3.506, p = .001) subscales. MS patients also reported marginally lower sleep quality compared to controls, t(37) = 2.026, p = .050.
Table 9. Summary of self ratings on quality of life (mood and sleep quality) indices in MS patients and controls

<table>
<thead>
<tr>
<th></th>
<th>MS patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>POMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension-Anxiety</td>
<td>13.0</td>
<td>13.1</td>
</tr>
<tr>
<td>Dejection-Depression</td>
<td>12.5</td>
<td>14.6</td>
</tr>
<tr>
<td>Anger-Hostility</td>
<td>8.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Vigour-Activity</td>
<td>14.5</td>
<td>15.1</td>
</tr>
<tr>
<td>Fatigue-Inertia</td>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Confusion-Bewilderment</td>
<td>10.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Total Mood Disturbance</td>
<td>39.0</td>
<td>44.1</td>
</tr>
<tr>
<td>PSQI Global Score</td>
<td>10.0</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Boxed values indicate differences significant at p < .05. Shaded boxed values indicate marginally significant (.05 < p < .10) differences.

4.1.1.1 Relations among SART indices

Controls with higher rates of No-go commission errors also made more omission errors on Go trials (r = .872, p = .001). Rates of both error types were greater in controls with (a) faster mean RT (r = -.873, p = .001, and r = -.819, p = .004, respectively) and (b) more variable responding (cvRT; r = .853, p = .002, and r = .845, p = .002, respectively). Pre-to-post commission error RT change (PES) was not related to other performance indicators (all p’s > .4). As seen in Table 7, this sample of controls, on average, showed negligible post-error slowing.

In MS patients, commission and omission error rates were not significantly related (p > .3). Patients having slower mean RT made more omission errors (r = .425, p = .022), but fewer commission errors (r = -.494, p = .006) and showed more post-error slowing, r = .554, p = .002. Greater response variability (cvRT) associated with both omission errors, r = .600, p = .001, and (marginally) commission errors, r = .361, p = .054.
4.1.1.2 Relations within neuropsychological measures

In controls, behavioural PLS yielded one significant LV (permuted p < .018, accounting for 88% of the cross-block covariance) relating cognitive test scores to self-reported daily cognitive dysfunction. Bootstrap estimated confidence intervals indicated that greater self-rated cognitive dysfunction corresponded to poorer performance on the Shipley as well as forward Digit Span, FAS, SART commission errors, the TEA (subtests 4 and 5) and deviation from optimal task timing on the Hotel Test. The inverse relation was seen for indices on the Tower Test, Trail-Making (time to complete B – A) and SDMT (oral). Within the MS patient group, a similar behavioural PLS analysis produced no significant LV (permuted p > .4).

Behavioural PLS relating cognitive test scores and informant-rated cognitive dysfunction did not reach significance in either patient or control groups (permuted p’s > .2 and .1, respectively).

MS patients’ self and informant ratings of cognitive dysfunction were related by one LV (permuted p < .0001, accounting for 96% of the cross-block covariance) with significant correlations for all subscales except DEX Negative Affect. Associations did not reach significance in controls (permuted p > .4).

Overall relations between cognitive test scores and self-rated mood and sleep quality did not reach significance in either patient or control groups (permuted p’s > .1).

MS patients’ self-rated cognitive dysfunction was directly associated with self-reported mood disturbance on the POMS Tension-Anxiety, Dejection-Depression and Anger-Hostility subscales as well as greater Fatigue and Confusion-Bewilderment (permuted p < .002, accounting for 93% of the cross-block covariance, Figure 3). Similarly robust relations were seen within the control group (permuted p < .004, accounting for 95% of the cross-block covariance) and included poorer self-reported sleep quality. Parallel relations to informant-rated cognitive dysfunction were not significant in controls (permuted p > .4), however in MS patients informant-rated deficits related significantly to Tension-Anxiety, Anger-Hostility, Fatigue and Confusion-Bewilderment (permuted p < .01, accounting for 97% of the cross-block covariance).
Figure 3. MS patients’ self-rated executive-attentional impairment in relation to reported mood disturbance and fatigue

4.1.2 Within-group effects of MS disease characteristics

As indicated in Table 10, the MS patient group contained roughly equal numbers of patients with relapsing-remitting and secondary progressive disease. These subgroups were matched demographically in terms of education, t(27) = .579 (p > .5), and female-to-male ratio, χ² = .082 (p > .7). As expected, patients with progressive disease were older, t(27) = 2.249, p = .033, and had longer disease duration, t(27) = 2.375, p = .025, and greater neurological disability (EDSS),
Mann-Whitney U = 50.0, p = .017. Using partial correlations to control for patient age, neurological disability (EDSS) was directly related to disease duration, r = .653, p < .001. Controlling for disease duration, age was not independently related to EDSS (p > .5).

Table 10. Disease characteristics in the MS patient group

<table>
<thead>
<tr>
<th>MS Subtype</th>
<th>n</th>
<th>Age * (years)</th>
<th>Education (years)</th>
<th>F : M</th>
<th>Disease duration * (years)</th>
<th>EDSS *</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>16</td>
<td>48.1</td>
<td>15.9</td>
<td>13 : 3</td>
<td>10.1</td>
<td>6.0</td>
</tr>
<tr>
<td>SP</td>
<td>13</td>
<td>56.4</td>
<td>16.5</td>
<td>10 : 3</td>
<td>18.3</td>
<td>12.1</td>
</tr>
</tbody>
</table>

* Group differences significant at p < .05

Behavioural PLS showed a marginal association between disease severity and performance on cognitive tests (permuted p < .086, accounting for 59% of the crossblock covariance). As shown in Figure 4, greater disease progression (neurological disability as indexed by EDSS) associated with poorer performance in both diagnostic groups, with a further effect of disease duration for patients with progressive but not relapsing-remitting disease. Bootstrap ratios indicated significantly impaired performance (with a 95% confidence interval) on the PASAT, SDMT, Trails (switching cost Time B-A), FAS (total correct), SART, TEA-3 and -5, Tower (total achievement and rule violations) and Hotel Test (number of tasks attempted and deviation from optimal time on task) with greater disease severity. For the SART, disease severity associated with significantly greater errors of both types (commission and omission) as well as greater reaction time variability (cvRT) but also greater post-error reaction time slowing (PES).
Figure 4. Impact of MS disease severity on cognitive measures

RR = relapsing-remitting MS; SP = secondary-progressive MS; EDSS = Expanded Disability Severity Scale

$r$ = test scores reverse-coded such that positive values correspond to better performance on all tests

Lower BSR values = greater impairment
Disease duration and neurological disability were marginally related to greater self-reported executive dysfunction (on all DEX subscales but not the CFQ) in patients with progressive disease (permuted p < .088, accounting for 64% of the crossblock covariance). However, following removal of an outlier (Appendix 2) this analysis did not reach significance (permuted p > .1). Disease characteristics were not reliably related to informant-rated cognitive dysfunction in either diagnostic group (permuted p > .1). Patients with progressive MS of longer duration and with greater neurological disability reported greater mood disturbance (permuted p < .006, 94% of covariance explained). Bootstrap ratios were significant (with a 95% confidence interval) for all POMS subscales but not for the PSQI (Figure 5). Correlations with disease duration and severity did not reach significance in patients with relapsing-remitting MS.

**Figure 5. Impact of MS disease severity on self-rated quality of life indices (mood and sleep disturbance)**

RR = relapsing-remitting MS; SP = secondary-progressive MS; EDSS = Expanded Disability Severity Scale
Higher BSR values = greater self-reported impairment
4.2 Effects of MS on neurophysiological correlates of attention and executive control

Mean amplitudes for the ERPs of interest (P3, ERN, Pe) for each ROI and SART trial type in neurologically healthy controls and MS patients (by diagnostic subtype) are summarized in Table 11.

Table 11. Mean amplitudes for ERPs of interest by ROI, trial type and group

<table>
<thead>
<tr>
<th>SART Trial Type</th>
<th>Group</th>
<th>L-Fr</th>
<th>Fr-C</th>
<th>R-Fr</th>
<th>L-Par</th>
<th>C-Par</th>
<th>R-Par</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct Go</td>
<td>cMS</td>
<td>0.48</td>
<td>0.87</td>
<td>0.72</td>
<td>1.25</td>
<td>1.07</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>RRMS</td>
<td>0.18</td>
<td>0.81</td>
<td>0.52</td>
<td>1.38</td>
<td>1.17</td>
<td>1.29</td>
</tr>
<tr>
<td></td>
<td>SPMS</td>
<td>1.11</td>
<td>1.33</td>
<td>0.98</td>
<td>1.11</td>
<td>0.68</td>
<td>0.69</td>
</tr>
<tr>
<td>Go (omission) error</td>
<td>cMS</td>
<td>0.77</td>
<td>0.52</td>
<td>0.15</td>
<td>1.77</td>
<td>0.90</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>RRMS</td>
<td>-0.68</td>
<td>0.15</td>
<td>-0.28</td>
<td>1.04</td>
<td>1.07</td>
<td>1.53</td>
</tr>
<tr>
<td></td>
<td>SPMS</td>
<td>0.79</td>
<td>-0.01</td>
<td>-0.01</td>
<td>1.32</td>
<td>0.65</td>
<td>0.40</td>
</tr>
<tr>
<td>Correct No-go (&quot;Stop&quot;)</td>
<td>cMS</td>
<td>2.62</td>
<td>4.19</td>
<td>2.46</td>
<td>4.18</td>
<td>5.22</td>
<td>4.24</td>
</tr>
<tr>
<td></td>
<td>RRMS</td>
<td>1.65</td>
<td>2.11</td>
<td>0.68</td>
<td>3.29</td>
<td>3.73</td>
<td>2.24</td>
</tr>
<tr>
<td></td>
<td>SPMS</td>
<td>2.91</td>
<td>1.88</td>
<td>0.93</td>
<td>2.90</td>
<td>2.23</td>
<td>1.51</td>
</tr>
<tr>
<td>No-go (commission) error</td>
<td>cMS</td>
<td>1.74</td>
<td>2.30</td>
<td>1.90</td>
<td>1.40</td>
<td>2.12</td>
<td>1.79</td>
</tr>
<tr>
<td></td>
<td>RRMS</td>
<td>1.41</td>
<td>1.61</td>
<td>1.29</td>
<td>1.05</td>
<td>1.72</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>SPMS</td>
<td>3.28</td>
<td>1.56</td>
<td>2.41</td>
<td>0.67</td>
<td>-0.54</td>
<td>-0.52</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ERN</th>
<th>Pe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error-response-related</td>
<td>cMS</td>
<td>-1.94</td>
</tr>
<tr>
<td>(No-go Error – Go Correct)</td>
<td>RRMS</td>
<td>-2.55</td>
</tr>
<tr>
<td></td>
<td>SPMS</td>
<td>-3.03</td>
</tr>
</tbody>
</table>

cMS = neurologically healthy controls; RRMS = relapsing-remitting MS patients; SPMS = secondary progressive MS patients; ERN = error-related negativity; Pe = error-related positivity

P3 ROIs: L-Fr = left frontal; Fr-C = fronto-central; R-Fr = right frontal; L-Par = left parietal; C-Par = centro-parietal; R-Par = right parietal
4.2.1 ERPs in neurologically healthy controls

4.2.1.1 P3

Controls’ ERP waveforms within the P3 time window for correct and inaccurate Go and No-go SART trials in the six P3 ROIs are presented together for comparison in Figure 6.

Figure 6. Stimulus-locked ERP waveforms by SART trial type and accuracy in the P3 ROIs for neurologically healthy controls

---

Go Correct

Go "Omission Error"

NoGo Correct ("Stop")

NoGo "Commission Error"
Mean amplitude differences in the P3 component for (correct) SART No-go compared to Go trials were analyzed using within-subject ANOVA with Trial Type (Go, No-go) and ROI (fronto-central, left and right frontal, centro-parietal, left and right parietal) as factors. Main effects were seen for Trial Type, $F(1,9) = 48.965, p < .001$, and ROI, $F(5,5) = 8.169, p = .019$, with a Trial Type by ROI interaction, $F(5,5) = 15.106, p = .005$. The No-go N2-P3 complex was clearly visible within all but the left frontal ROI waveforms, and simple effects tests showed mean amplitudes were significantly or marginally greater on correct No-go compared to Go trials at all ROIs (all $p$’s < .052). Comparison of incorrect No-go trials to correct Go trials did not reach significance ($p > .1$).

The Trial Type by ROI ANOVA comparing correct and incorrect No-go trials (i.e. Stops and Commission Errors) found an effect of Trial Type, $F(1,9) = 18.657, p = .003$, and of ROI, $F(5,5) = 14.398, p = .011$, with a marginal Trial Type by ROI interaction, $F(5,5) = 5.782, p = .057$. Simple effects tests showed significantly or marginally greater ERP amplitudes on No-go Stop compared to Error trials in the following ROIs: fronto-central, $t(9) = 2.266, p = .053$; left frontal, $t(9) = 1.976, p = .084$; centro-parietal, $t(9) = 3.680, p = .006$; right parietal, $t(9) = 3.879, p = .005$; and left parietal, $t(9) = 5.422, p = .001$.

Comparison of correct and incorrect Go trials revealed no significant differences in P3 amplitudes ($p > .1$).

Likewise, no significant amplitude differences were seen for Go trials preceding a No-go Stop compared to a commission Error ($p > .4$) or for Go trials following a Stop compared to an Error ($p > .1$). Amplitude differences between Go trials post- compared to pre-Error also did not reach significance ($p > .1$).

### 4.2.1.2 ERN and Pe

A paired t-test comparing mean response-linked amplitudes on No-go Error compared to Correct Go trials showed a significant ERN for No-go commission Errors at the relevant fronto-central ROI, $t(9) = 3.752, p = .005$ (Figure 7a). A significant Pe was also seen at the centro-parietal ROI, $t(9) = 2.370, p = .042$ (Figure 7b).
Figure 7. Responselocked error-related ERP waveforms for neurologically healthy controls

(a) In the fronto-central error-related negativity (ERN) ROI

(b) In the centro-parietal error-related positivity (Pe) ROI
4.2.2 ERPs in MS patients

4.2.2.1 P3

MS patients’ ERP waveforms for correct and inaccurate Go and No-go SART trials in the 6 P3 ROIs are presented together for comparison in Figure 8.

Mean amplitude differences in the P3 component for (correct) SART No-go compared to Go trials were analyzed using within-subject ANOVA with Trial Type (Go, No-go) and ROI (Fronto-central, Left and Right frontal, Centro-parietal, Left and Right parietal) as factors. Main effects were seen for Trial Type, F(1,28) = 18.824, p < .001, and ROI, F(5,24) = 6.750, p < .001, with a Trial Type by ROI interaction, F(5,24) = 9.837, p < .001. Simple effects tests showed mean amplitudes were significantly greater on correct No-go compared to Go trials in the following ROIs: fronto-central, t(28) = 2.104, p = .044; left frontal, t(28) = 5.032, p < .001; centro-parietal, t(28) = 4.654, p < .001; left parietal, t(28) = 5.490, p < .001; and right parietal ROI, t(28) = 2.875, p = .008. Comparison of incorrect No-go trials to correct Go trials also yielded a main effect of Trial Type, F(1,28) = 5.293, p = .029, however simple effects tests showed that mean amplitudes in the P3 window were significantly greater on No-go Error trials only in the left frontal ROI, t(28) = 3.823, p = .001 (p’s for all other ROIs > .1).

Another Trial Type by ROI ANOVA comparing correct and incorrect No-go trials (i.e. Stops and Commission Errors) found a significant effect of Trial Type, F(1,28) = 7.405, p = .011 and ROI, F(5,24) = 2.825, p = .039, with a marginal interaction, F(5,24) = 2.604, p = .052. Simple effects tests showed greater mean amplitudes on correct No-go trials in the parietal ROIs: centro-parietal, t(28) = 3.439, p = .002; left parietal, t(28) = 2.754, p = .010; and right parietal, t(28) = 2.591, p = .015.

Comparison of correct and incorrect Go trials revealed marginal effects of Trial Type, F(1,27) = 4.108, p = .053, and ROI, F(5,23) = 2.458, p = .063, qualified by a Trial Type by ROI interaction, F(5,23) = 2.759, p = .043. As shown in Figure 8, greater amplitudes on correct trials were seen in the frontal ROIs, however simple effects tests approached significance only for the fronto-central ROI, t(27) = 1.839, p = .077.
Figure 8. Stimulus-locked ERP waveforms by SART trial type and accuracy in the P3 ROIs for MS patients.
A significant effect of ROI in P3 amplitude differences between Go trials preceding (F(5,24) = 4.206, p = .007) and following (F(5,24) = 3.010, p = .030) No-go Stops compared to Errors were driven by greater overall amplitudes in the fronto-central and left parietal ROIs (across trial types). Comparison of amplitude differences between Go trials post- compared to pre-Error revealed a similar effect of ROI only, F(5,24) = 3.707, p = .013.

Figure 9. Response-locked error-related ERP waveforms for MS patients

(a) In the fronto-central error-related negativity (ERN) ROI

(b) In the centro-parietal error-related positivity (Pe) ROI
4.2.2.2 ERN and Pe

A paired t-test comparing mean response-linked amplitudes on No-go Error compared to Correct Go trials showed a significant ERN for No-go commission Errors at the relevant fronto-central ROI, \( t(28) = 4.044, p < .001 \) (Figure 9a). A subsequent positivity was visible in the patient group’s No-go error response waveform (Figure 9b), however its amplitude (\( M = 1.707 \mu V \)) was not significantly greater (\( p > .4 \)) than that of the correct Go response (\( M = 1.250 \mu V \)), indicating no significant Pe in the patient group.

4.2.3 Comparison of MS patients and controls
4.2.3.1 P3, ERN and Pe amplitudes

P3 latencies were, as expected, delayed in MS patients relative to controls. For example, on correct No-go trials (which featured the most distinct P3 peaks in all participants) a main effect of Group, \( F(1,37) = 12.594, p = .001 \) (with no effect of ROI nor interaction effect) reflected significantly slower peak latencies for MS patients in all ROIs (t-tests all \( p’s < .02 \)).

Topographic maps of mean P3 amplitudes by SART trial type and accuracy for controls and patients (by clinical subtype) are shown in Figure 10. Groups showed similar Go-linked scalp distributions with a slight anterior and left-lateral shift in progressive patients. The No-go P3 was attenuated and left-lateralized in MS patients relative to the centro-parietal peak seen in controls.

Mean-centered PLS comparing controls’ and MS patients’ mean amplitudes in the ERPs of interest (i.e., correct Go and No-go P3, ERN and Pe) yielded one marginally significant LV (permuted \( p < .0898 \), Figure 11). Relative to MS patients, controls had greater P3 amplitudes in the right frontal ROI on SART Go trials in addition to increasingly greater No-go amplitudes from the left through to right parietal ROIs and the fronto-central ROI. Pe amplitudes were also greater in controls relative to patients (refer back to Table 11). Only in the left parietal ROI during SART Go trials did patients have reliably greater P3 amplitudes compared to controls.
Figure 10. Topographic maps of mean P3 amplitudes (μV) in neurologically healthy controls and MS patients

Controls  RRMS  SPMS

Go
Correct

Go
“Omission
Error”

NoGo
Correct
(“Stop”)

NoGo
“Commission
Error”

RRMS = relapsing-remitting; SPMS = secondary-progressive MS patients
Figure 11. Comparison of SART mean ERP amplitudes (P3, ERN and Pe) between controls and MS patients (mean-centered PLS)

All ERPs coded such that greater positive values corresponded to greater mean amplitudes (i.e. greater positive P3 and Pe amplitudes and greater negative ERN amplitudes)

P3 ROIs: L-Fr = left frontal; Fr-C = fronto-central; R-Fr = right frontal; L-Par = left parietal; C-Par = centro-parietal; R-Par = right parietal

Behavioural PLS further assessed the influence of disease duration and neurological symptom severity on mean ERP amplitudes. Go and No-go P3 amplitudes in all frontal and parietal ROIs, though most robustly in the right-to-central parietal ROIs and the fronto-central ROI, were attenuated as a function of neurological disability (EDSS) in all patients as well as disease
duration in progressive patients (permuted p < .040, accounting for 73% of the cross-block covariance, Figure 12). The high bootstrap ratios for the central and right parietal ROIs were not attributable to an outlier effect (Appendix 3). Greater MS disease severity also associated with reduced Pe but not ERN amplitudes.

**Figure 12. Impact of MS disease severity on mean ERP amplitudes (behavioural PLS)**

All ERPs coded such that greater positive values corresponded to greater mean amplitudes (i.e. greater positive P3 and Pe amplitudes and greater negative ERN amplitudes)

P3 ROIs: L-Fr = left frontal; Fr-C = fronto-central; R-Fr = right frontal; L-Par = left parietal; C-Par = centro-parietal; R-Par = right parietal
### 4.2.3.2 Relation of ERPs to task performance

Behavioural PLS comparing SART P3-behaviour patterns in controls and MS patients yielded two significant LVs. The first (permuted p < .0001, accounting for 62% of the cross-block covariance, Figure 13) contrasted patients and controls. Lower parietal P3 amplitudes, most robustly on Go trials, as well as fronto-central P3 amplitudes on both trial types associated with better SART performance (fewer commission errors and greater RT stability) in controls but poorer performance (more omission errors and RT variability) in patients. The second LV (permuted p < .002, accounting for 29% of the cross-block covariance, Figure 14) related greater frontal P3 amplitudes (both trial types) to lower omission errors and RT variability in the patient group. Similar to the correlations between SART behavioural indices reported above (Section 4.1.1.1), slower mean RT associated with better performance (accuracy and stability) in controls but worse performance in patients.

P3 amplitude increases on Go trials from pre-to-post commission error differentially related to SART behavioural indices in controls compared to patients (permuted p < .002, accounting for 66% of the cross-block covariance, Figure 15). Particularly in the left and central parietal ROIs (but significantly in all but the right frontal ROI), P3 amplitude increases associated with post-error slowing but no other SART behavioural indices in controls. In patients, this pattern of amplitude increases associated with slower mean RT and fewer commission errors however with higher rates of omission errors.

ERN but not Pe amplitudes related to lower commission and omission errors and greater RT stability in both patients and controls (permuted p < .016, Figure 16). As with the SART behavioural correlations and P3-behaviour analyses, slower mean RT associated with better performance (accuracy and stability) in controls but worse performance (though not reaching multivariate significance in this analysis) in patients.
Figure 13. Relation of SART Go and No-go P3 amplitudes to task performance in neurologically healthy controls and MS patients (behavioural PLS): LV1

ERPs coded such that greater positive values corresponded to greater mean amplitudes
SART behavioural indices are raw-coded

P3 ROIs: L-Fr = left frontal; Fr-C = fronto-central; R-Fr = right frontal; L-Par = left parietal; C-Par = centro-parietal; R-Par = right parietal
Figure 14. Relation of SART Go and No-go P3 amplitudes to task performance in neurologically healthy controls and MS patients (behavioural PLS): LV2

ERPs coded such that greater positive values corresponded to greater mean amplitudes
SART behavioural indices are raw-coded
Figure 15. Relation of SART post-error P3 amplitude changes to task performance in neurologically healthy controls and MS patients (behavioural PLS)

ERPs coded such that positive values corresponded to mean P3 amplitudes increases
SART behavioural indices are raw-coded
Figure 16. Relation of SART No-go error-related (ERN, Pe) amplitude changes to task performance in neurologically healthy controls and MS patients (behavioural PLS)

ERPs coded such that greater positive values corresponded to greater mean amplitudes (i.e. greater positive Pe and greater negative ERN amplitudes)

SART behavioural indices are raw-coded
4.2.3.3 Relation of ERPs to broader neuropsychological performance

Beyond the relation to performance on the EEG task itself (i.e., the SART) behavioural PLS also linked mean P3 amplitudes to performance across the battery of cognitive tests completed “offline” (permuted p < .0001, accounting for 40% of the cross-block covariance). Correlations indicated this broader relation of P3 amplitudes to cognitive performance was significant for the MS patients moreso than controls. Patients with greater frontal amplitudes on both Go and No-go trials and greater No-go parietal amplitudes performed better on tests including the PASAT, Digit Span forward, SDMT, Trails, FAS, TEA-3 and Tower Test (Figure 17).

Figure 17. Relation of SART Go and No-go P3 amplitudes to test performance in the broader neuropsychological battery in controls and MS patients (behavioural PLS)
(a) In neurologically healthy controls

(b) In MS patients

$r = \text{test scores reverse-coded such that positive values correspond to better performance on all tests}$

$\text{ERPs coded such that greater positive values corresponded to greater mean amplitudes}$
ERN but not Pe amplitudes related to better test performance in both controls and MS patients (permuted p < .012, accounting for 51% of the cross-block covariance). Participants with greater ERN amplitudes performed better on Trails (time B-A), TEA-4 and 5, Tower and Hotel Tests as well as having greater estimated verbal intelligence (Shipley) and better performance on SART behavioural indices (i.e., accuracy, RT stability and post-error slowing) (Figure 18). No clear outliers were visible to explain the high bootstrap ratios (Appendix 4).

**Figure 18. Relation of SART No-go error-related (ERN, Pe) amplitudes to broader test performance in the broader neuropsychological battery in controls and MS patients (behavioural PLS)**

$r$ = test scores reverse-coded such that positive values correspond to better performance on all tests

ERPs coded such that greater positive values corresponded to greater mean amplitudes
Chapter 5
Results: Rehabilitation of executive dysfunction in MS

5.1 Patient group characteristics

Of the 29 MS patients initially recruited, 28 were enrolled in the rehabilitation trial with 14 receiving GMT and 14 receiving BHW. One participant in the GMT group experienced a fall and mild traumatic head injury (with evidence of small posterior hemorrhage on clinical imaging) prior to completing post-training assessment and could not continue participation. As a result, post-training data were available for only 13 GMT patients. Three additional study participants were lost to attrition prior to the 6-month follow-up test session, two within the GMT group (one who developed a new illness, the other citing personal reasons) and one within the BHW group (also for personal reasons). One additional participant in the BHW group was non-cooperative and failed to complete a majority of the outcome measures. The DEX (self) was incomplete for one GMT patient (at post-training). Informants failed to return their ratings (DEX other) for three GMT and two BHW patients (at post-training and/or follow-up). Data for most tests at each of the baseline, post-training and 6-month follow-up assessments were available for 11 GMT patients and 12 BHW patients. As seen in Table 12, the intervention groups were matched on disease characteristics and demographics with the exception of an incidental group difference in education; GMT patients had greater mean education compared to the BHW group, \( t(21) = 2.467, p = .022 \). No other group differences were significant (p's > .2).

Given the incidental group difference on education, correlations between education and neuropsychological measures were explored. No significant relation of education to outcome variable scores (at baseline) were seen (p's > .1) with the exception of better sleep quality (lower PSQI global score) in patients having more years of education, \( r = -.372, p = .047 \). Education was also unrelated to degree of change (from baseline to post-training or baseline to follow-up) on most outcome measures (p's > .1). Higher education was associated with greater baseline to post-training improvement on the TEA (subtest 3), \( r = .496, p = .009 \), but decreased self-reported POMS vigour (\( r = -.375, p = .065 \)) and PSQI global sleep quality (\( r = -.499, p = .009 \)). Decline in vigour (\( r = -.390, p = .081 \)) and sleep quality (\( r = -.535, p = .012 \)) was also seen in the more educated patients from baseline to 6-month follow-up. Analyses of group outcomes on the TEA
3. POMS vigour subscale and PSQI were therefore checked using ANCOVAs, with Education as a covariate, and these results compared to the planned ANOVAs as reported below.

Patients’ attendance to the group sessions was similar for both groups, with a total of 6 missed sessions among individual GMT patients and 7 sessions among BHW patients for a group attendance rate of 95.2% and 94.4% respectively. Patients who missed a group session all completed individual make-up sessions with the trainer prior to the next scheduled group module. Their outcome results were not distinguishable from those of their overall group.

Table 12. Demographic data for MS patients completing the rehabilitation trial

<table>
<thead>
<tr>
<th></th>
<th>GMT</th>
<th>BHW</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>RR : Prog</td>
<td>7 : 4</td>
<td>7 : 5</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>EDSS</td>
<td>3.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.1</td>
<td>52.4</td>
</tr>
<tr>
<td>Education (years)</td>
<td>17.3 *</td>
<td>14.8 *</td>
</tr>
</tbody>
</table>

* Group differences significant at p < .05

5.2 Cognitive test performance

Scores on the cognitive outcome measures including functional-behavioural tests are summarized by intervention group and test time in Table 13 together with effect sizes (d) for the changes (compared to baseline) in these variables at post-training and follow-up within each intervention group.
Table 13. Performance on cognitive outcome measures in the patient intervention groups

<table>
<thead>
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<th>GMT</th>
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<th>Omnibus</th>
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<td></td>
<td>Mean</td>
<td>SD</td>
<td>d</td>
</tr>
<tr>
<td></td>
<td>(Median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tx*</td>
<td>Time</td>
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<tr>
<td><strong>SART</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Commission Errors (%) No-go trials</td>
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<td></td>
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<tr>
<td>Baseline</td>
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<tr>
<td>Post-training</td>
<td>39.4</td>
<td>29.6</td>
<td>.29</td>
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<tr>
<td>Follow-up</td>
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<tr>
<td>Omission Errors (%) Go trials</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.4</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Post-training</td>
<td>4.4</td>
<td>4.7</td>
<td>.22</td>
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<tr>
<td>Follow-up</td>
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<td>3.3</td>
<td>.43</td>
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<tr>
<td>Mean RT (msec)</td>
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</tr>
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<td>.10</td>
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<tr>
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<tr>
<td>RT Coefficient of Variation</td>
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<td>.06</td>
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<td>Post-Error Slowing (msec)</td>
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<td>Baseline</td>
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<td><strong>TEA</strong></td>
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<td>3: Elevator Counting with Distraction</td>
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<td>.33</td>
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<td>4: Visual Elevator</td>
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<td>5: Elevator Counting with Reversal</td>
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<td>.27</td>
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<td>Move Accuracy Ratio</td>
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<tr>
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<tr>
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<td>0.4</td>
<td>.46</td>
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<tr>
<td>Follow-up</td>
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<td>0.6</td>
<td>.77</td>
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<tr>
<td>Rule Violations</td>
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</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Post-training</td>
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<tr>
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### Hotel Task

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<tr>
<th># Tasks Attempted</th>
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<th>4.2</th>
<th>1.2</th>
<th>4.2</th>
<th>1.1</th>
<th>n.s.</th>
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<td>Post-training</td>
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<td>4.3</td>
<td>1.0</td>
<td>.15</td>
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<td>Follow-up</td>
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<td>.85</td>
<td>*</td>
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<td>0.7</td>
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### Deviation from Optimal Task Time (sec)

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<th>Baseline</th>
<th>495.7</th>
<th>260.9</th>
<th>509.8</th>
<th>290.3</th>
<th>n.s.</th>
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<tr>
<td>Post-training</td>
<td>403.6</td>
<td>111.7</td>
<td>.46</td>
<td>458.3</td>
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<td>.22</td>
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<tr>
<td>Follow-up</td>
<td>345.3</td>
<td>116.1</td>
<td>.69</td>
<td>406.2</td>
<td>144.1</td>
<td>.45</td>
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</table>

### Garage Deviation Score

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<th>(7.0)</th>
<th>(6.5)</th>
<th>n/a</th>
<th>n/a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-training</td>
<td>(8.0)</td>
<td>(7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>(8.0)</td>
<td>(8.0)</td>
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### Goal Attainment Score

<table>
<thead>
<tr>
<th>Post-training increase in goal attainment level (untrained goals)</th>
<th>(3.0)</th>
<th>(2.0)</th>
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<th>n/a</th>
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</table>

Effect sizes (d) in parentheses indicate worse scores relative to baseline, across-group change relative to baseline indicated by * (p < .05) or ± (.05 < p < .10) (Bonferroni-corrected). Within-group change relative to baseline indicated by boxed values (p < .05) or shaded values (.05 < p < .10) (uncorrected). † Wilcoxon signed-ranks test in lieu of parametric.

Group scores on SART measures at baseline, post-training and 6-month follow-up are illustrated in Figure 19. A main effect of Time (with no significant Time by Treatment interaction) was seen for SART omission errors, F(2,44) = 4.852, p = .012, ηp² = .181, with decreased errors (across groups) from baseline to follow-up, p = .013 (Bonferroni-corrected). A main effect of Time also obtained for RT variability (cvRT), F(1.58, 44) = 3.371, p = .056, ηp² = .133, with decreased RT variability (across groups) from baseline to post-training, p = .044 (Bonferroni-corrected). Omnibus analyses did not reach statistical significance for SART commission errors, mean RT or post-error slowing (p’s > .1).

---

5 Greenhouse-Geisser correction applied.
Figure 19. Intervention group outcomes on SART indices

(a) Commission errors (% No-go trials)  
(b) Omission errors (% Go trials)

(c) RT variability (correct Go trials)  
(d) Post-No-go-error RT slowing

Group scores on each of the three subtests of the Test of Everyday Attention (TEA) at baseline, post-training and 6-month follow-up are illustrated in Figure 20. Omnibus analysis of change in TEA 3 scores did not reach statistical significance whether using ANOVA or ANCOVA with education as a covariate (p’s > .2). A main effect of Time (with no significant Time by Treatment interaction) was seen on the TEA 4, F(2,42) = 7.827, p = .001, \( \eta_p^2 = .272 \), with improved scores (across groups) from baseline to follow-up, p = .001 (Bonferroni-corrected). A marginal Time by Treatment interaction obtained for the TEA 5, F(2,40) = 3.099, p = .056, \( \eta_p^2 = .134 \). As shown in Table 13 and Figure 20, TEA 5 scores improved in the GMT group but declined in the BHW group.
Figure 20. Intervention group outcomes on Test of Everyday Attention subtests

(a) TEA-3 (selective attention)

(b) TEA-4 (attentional switching)

(c) TEA-5 (attentional switching, working memory)

Group scores on Tower Test measures at baseline, post-training and 6-month follow-up are shown in Figure 21. A marginally significant effect of Time was seen on the total achievement score, $F(2, 44) = 2.478$, $p = .096$, $\eta_p^2 = .101$. As shown in Table 13 and Figure 21 this reflected a trend toward improvement at post-training and follow-up in both intervention groups, however Bonferroni-corrected contrasts did not reach statistical significance. A significant effect of Time on the Tower Test move-accuracy ratio, $F(2, 44) = 4.475$, $p = .017$, $\eta_p^2 = .169$, was seen with improved scores (across groups) from baseline to follow-up, $p = .035$ (Bonferroni-corrected). Tower rule violations were significantly reduced at post-training and follow-up in the GMT group ($Z = 2.958$, $p = .003$, and $Z = 2.567$, $p = .010$) and BHW group ($Z = 3.210$, $p = .001$, and $Z = 2.950$, $p = .003$).
5.2.1 Functional-behavioural measures

Group scores on Hotel Test measures at baseline, post-training and 6-month follow-up are illustrated in Figure 22. A significant effect of Time was seen on the number of tasks attempted in the Hotel Test, F(1,23,42) = 5.247, p = .024, $\eta^2_p = .200$, with improved scores (across groups) from baseline to follow-up, p = .037 (Bonferroni-corrected). A marginally significant effect of Time was also seen on deviation from optimal time on task, F(2,42) = 2.988, p = .061, $\eta^2_p = .125$. As shown in Table 13 and Figure 22 this reflected a trend toward improvement at post-training and follow-up in both intervention groups, however Bonferroni-corrected contrasts did not reach statistical significance. Garage deviation scores on the Hotel Test were not significantly different from baseline in either group at post-training or follow-up (p’s > .3, Figure 22c).
Both the GMT group ($Z = 2.958, p = .003$) and BHW group ($Z = 2.988, p = .003$) reported improved attainment on untrained goals post-intervention, but with significantly greater change following GMT compared to BHW, $U = 36.0, p = .035$ (Figure 23). No improvement was seen in two BHW patients (14.3%) whereas all patients in the GMT group improved by at least one scale level. Seven GMT patients exceeded their target goal (53.9%), three of whom reached their ideal goal. In the BHW group, three patients (21.4%) exceeded target and none reached their ideal goal attainment. There was no difference in the degree of GMT patients’ improvement on their trained compared to untrained goals ($Z = 1.589, p > .1$).
Figure 23. Intervention group outcomes on Goal Attainment Scaling
5.3 Self- and informant-rated daily executive functioning

Self- and informant-ratings on the real-life executive dysfunction questionnaires are summarized by intervention group and test time in Table 14 together with effect sizes (d) for the changes (compared to baseline) in these variables at post-training and follow-up within each intervention group.

For self-rated functioning, a marginally significant effect of Time (with no significant Time by Treatment interaction) was seen on the Cognitive Failures Questionnaire, $F(2,42) = 2.813$, $p = .071$, $\eta_p^2 = .118$. As shown in Table 14 this reflected a trend toward improvement at post-training and follow-up in both intervention groups, however Bonferroni-corrected contrasts did not reach statistical significance. A significant or marginal effect of time also obtained on DEX subscales, including Inhibition, $F(2,44) = 4.069$, $p = .024$, $\eta_p^2 = .162$ (with improvement across groups from baseline to post-training, $p = .043$, corrected), Intention, $F(2,44) = 2.600$, $p = .086$, $\eta_p^2 = .106$, Executive Memory, $F(2,44) = 3.127$, $p = .054$, $\eta_p^2 = .124$, as well as self-rated DEX Total Score, $F(2,42) = 3.504$, $p = .039$, $\eta_p^2 = .143$. Omnibus effects on the DEX Positive and Negative Affect subscales did not reach statistical significance ($p > .1$).

Significant or marginal main effects of Time were also seen for patients’ observed (informant-rated) functioning on the DEX. These included subscale totals for Inhibition, $F(1.46,34) = 5.475$, $p = .018$, $\eta_p^2 = .244$ (with improvement across groups from baseline to follow-up, $p = .051$, and post-training to follow-up, $p = .069$, corrected), Intention, $F(2,34) = 8.510$, $p = .001$, $\eta_p^2 = .334$ (with improvement across groups from baseline to post-training, $p = .064$, and follow-up, $p = .007$, corrected), Executive Memory, $F(2,34) = 4.258$, $p = .022$, $\eta_p^2 = .200$ (with improvement across groups from post-training to follow-up, $p = .014$, corrected), as well as informant-rated DEX Total Score, $F(2,34) = 8.223$, $p = .001$, $\eta_p^2 = .326$ (with improvement across groups from baseline to follow-up, $p = .009$, and post-training to follow-up, $p = .033$, corrected). Marginally significant effects of Time were also seen on the Positive Affect, $F(2,34) = 2.847$, $p = .072$, $\eta_p^2 = .143$, and Negative Affect, $F(2,34) = 2.960$, $p = .065$, $\eta_p^2 = .148$, subscales.
Table 14. Self- and informant-rated cognitive outcomes in the patient intervention groups

<table>
<thead>
<tr>
<th></th>
<th>GMT</th>
<th>BHW</th>
<th>Omnibus p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>d</td>
</tr>
<tr>
<td><strong>CFQ</strong> (Self ratings)</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>44.9</td>
<td>17.6</td>
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</tr>
<tr>
<td>Post-training</td>
<td>42.3</td>
<td>11.3</td>
<td>.18</td>
</tr>
<tr>
<td>Follow-up</td>
<td>41.7</td>
<td>13.5</td>
<td>.20</td>
</tr>
<tr>
<td><strong>DEX (Self)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition Baseline</td>
<td>8.2</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Post-training</td>
<td>6.6</td>
<td>3.9</td>
<td>.34</td>
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<tr>
<td>Follow-up</td>
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<td>4.0</td>
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<tr>
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<td>3.3</td>
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<td>Follow-up</td>
<td>5.9</td>
<td>1.9</td>
<td>.28</td>
</tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Post-training</td>
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<td>2.1</td>
<td>.21</td>
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<tr>
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<td>1.9</td>
<td>.40</td>
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<tr>
<td>Negative Affect Baseline</td>
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<td></td>
</tr>
<tr>
<td>Post-training</td>
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<td>0.9</td>
<td>(.15)</td>
</tr>
<tr>
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<td>1.4</td>
<td>(.13)</td>
</tr>
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<tr>
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<td>Follow-up</td>
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</tr>
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<td><strong>DEX (Informant)</strong></td>
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<tr>
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<td>7.4</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Post-training</td>
<td>7.6</td>
<td>8.5</td>
<td>(.03)</td>
</tr>
<tr>
<td>Follow-up</td>
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<td>3.8</td>
<td>.53 ±</td>
</tr>
<tr>
<td>Intention Baseline</td>
<td>8.6</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Post-training</td>
<td>5.9</td>
<td>4.3</td>
<td>.51 ±</td>
</tr>
<tr>
<td>Follow-up</td>
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<td>3.1</td>
<td>.77 *</td>
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<tr>
<td>Executive Memory Baseline</td>
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<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Post-training</td>
<td>3.8</td>
<td>2.9</td>
<td>(.12)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.4</td>
<td>2.0</td>
<td>.44</td>
</tr>
<tr>
<td>Positive Affect Baseline</td>
<td>4.1</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Post-training</td>
<td>2.6</td>
<td>2.4</td>
<td>.52</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.5</td>
<td>2.2</td>
<td>.58</td>
</tr>
<tr>
<td>Negative Affect Baseline</td>
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<td>1.7</td>
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</tr>
<tr>
<td>Post-training</td>
<td>1.6</td>
<td>2.0</td>
<td>.32</td>
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<tr>
<td>Follow-up</td>
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<td>1.4</td>
<td>.63</td>
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<tr>
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<td>Post-training</td>
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<td>18.8</td>
<td>.24</td>
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<tr>
<td>Follow-up</td>
<td>15.7</td>
<td>10.4</td>
<td>.68 *</td>
</tr>
</tbody>
</table>

Effect sizes (d) in parentheses indicate worse scores relative to baseline, Across-group change relative to baseline indicated by * (p < .05) or ± (.05 < p < .10) (Bonferroni-corrected). Within-group change relative to baseline indicated by boxed values (p < .05) or shaded values (.05 < p < .10) (uncorrected), analyzed for informant ratings only.
5.4 Quality of life indicators: Self-reported mood and sleep quality

Self-ratings of mood and sleep quality are summarized by intervention group and test time in Table 15 together with effect sizes (d) for the changes (compared to baseline) in these variables at post-training and follow-up within each intervention group.

A significant main effect of Time was seen on the Profile of Mood States (POMS) total mood disturbance (across all subscales), \( F(1.32,38) = 5.799, p = .017, \eta_p^2 = .234 \) (with improvement across groups from baseline to post-training, \( p = .061 \), and follow-up, \( p = .061 \), corrected), as well as on individual subscales including Anxiety, \( F(1.35,38) = 4.646, p = .031, \eta_p^2 = .196 \) (with improvement across groups from baseline to follow-up, \( p = .080 \), corrected), Depression-Dejection, \( F(1.29,38) = 6.461, p = .012, \eta_p^2 = .254 \) (with improvement across groups from baseline to follow-up, \( p = .029 \), and post-training to follow-up, \( p = .047 \), corrected), Anger-Hostility, \( F(1.56,38) = 8.140, p = .003, \eta_p^2 = .300 \) (with improvement across groups from baseline to post-training, \( p = .012 \), and follow-up, \( p = .067 \), corrected), and Confusion-Bewilderment, \( F(2,38) = 6.129, p = .005, \eta_p^2 = .244 \) (with improvement across groups from baseline to post-training, \( p = .044 \), and follow-up, \( p = .041 \), corrected). A marginally significant effect of Time was seen on the POMS Fatigue-Inertia subscale, \( F(1.50,38) = 2.715, p = .096, \eta_p^2 = .125 \).

Sleep disturbance was reduced in both groups, with ANCOVA showing an effect of Time on the Pittsburgh Sleep Quality Index (PSQI) global score, \( F(2,36) = 8.562, p = .001, \eta_p^2 = .322 \) (with improvement across groups from baseline to post-training, \( p = .015 \), that was largely attenuated at follow-up, \( p = .096 \), corrected). This effect held without factoring out Education as a covariate (ANOVA \( p = .017 \)).
Table 15. Outcomes on self-rated quality of life indices in the patient intervention groups

<table>
<thead>
<tr>
<th>POMS</th>
<th>GMT</th>
<th></th>
<th>BHW</th>
<th></th>
<th>Omnibus p</th>
<th>T x*</th>
<th>Time</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
<td><strong>d</strong></td>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
<td><strong>d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension-Anxiety</td>
<td>Baseline 13.6</td>
<td>7.9</td>
<td>11.6</td>
<td>6.4</td>
<td>n.s.</td>
<td>.031</td>
<td></td>
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<tr>
<td></td>
<td>Post-training 10.4</td>
<td>3.4</td>
<td>9.7</td>
<td>5.5</td>
<td>.32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up 10.1</td>
<td>3.2</td>
<td>8.3</td>
<td>4.5</td>
<td>.59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dejection-Depression</td>
<td>Baseline 18.5</td>
<td>13.8</td>
<td>10.6</td>
<td>10.6</td>
<td>n.s.</td>
<td>.012</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Post-training 11.8</td>
<td>5.7</td>
<td>10.2</td>
<td>6.0</td>
<td>.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up 10.0</td>
<td>4.5</td>
<td>6.5</td>
<td>5.3</td>
<td>.48</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anger-Hostility</td>
<td>Baseline 13.1</td>
<td>8.3</td>
<td>7.6</td>
<td>10.4</td>
<td>n.s.</td>
<td>.003</td>
<td></td>
<td></td>
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<td>Post-training 6.8</td>
<td>3.6</td>
<td>4.0</td>
<td>4.1</td>
<td>.46</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Follow-up 11.2</td>
<td>6.6</td>
<td>5.2</td>
<td>7.1</td>
<td>.27</td>
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<td>Vigour-Activity</td>
<td>Baseline 15.5</td>
<td>7.4</td>
<td>14.2</td>
<td>5.3</td>
<td>n.s.</td>
<td>.062</td>
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<td>Post-training 14.8</td>
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<td>5.6</td>
<td>.29</td>
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<td></td>
<td>Follow-up 15.0</td>
<td>6.4</td>
<td>14.8</td>
<td>4.1</td>
<td>.14</td>
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<tr>
<td>Fatigue-Inertia</td>
<td>Baseline 12.3</td>
<td>4.3</td>
<td>9.8</td>
<td>5.6</td>
<td>n.s.</td>
<td>.096</td>
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<tr>
<td></td>
<td>Post-training 10.6</td>
<td>4.4</td>
<td>9.4</td>
<td>5.5</td>
<td>.07</td>
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<tr>
<td></td>
<td>Follow-up 9.0</td>
<td>4.7</td>
<td>8.1</td>
<td>3.9</td>
<td>.35</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Confusion-Bewilderment</td>
<td>Baseline 10.9</td>
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<td>8.9</td>
<td>5.3</td>
<td>n.s.</td>
<td>.005</td>
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<tr>
<td></td>
<td>Post-training 7.8</td>
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<td>7.1</td>
<td>3.0</td>
<td>.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up 8.6</td>
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<td>6.0</td>
<td>3.1</td>
<td>.67</td>
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<td></td>
<td></td>
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<tr>
<td>Total Mood Disturbance</td>
<td>Baseline 52.9</td>
<td>39.2</td>
<td>34.3</td>
<td>38.5</td>
<td>n.s.</td>
<td>.017</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Post-training 34.9</td>
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<td>23.0</td>
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<td>.36</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up 36.3</td>
<td>20.9</td>
<td>20.5</td>
<td>24.1</td>
<td>.43</td>
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</table>

**PSQI**

<table>
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<th>PSQI</th>
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<th></th>
<th>BHW</th>
<th></th>
<th>Omnibus p</th>
<th>T x*</th>
<th>Time</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
<td><strong>d</strong></td>
<td><strong>Mean</strong></td>
<td><strong>SD</strong></td>
<td><strong>d</strong></td>
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<td>Global Sleep Disturbance</td>
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<td>5.4</td>
<td>n.s.</td>
<td>.015</td>
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<td>Post-training 7.0</td>
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<td>5.6</td>
<td>.35</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Follow-up 7.9</td>
<td>3.3</td>
<td>6.6</td>
<td>3.8</td>
<td>.53</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effect sizes (d) in parentheses indicate worse scores relative to baseline. Across-group change relative to baseline indicated by * (p < .05) or ± (.05 < p < .10) (Bonferroni-corrected).
5.5 Composite scores and change scores

Patients’ composite change scores (Section 3.3.1.2.4) from baseline-to-post-training or baseline-to-follow-up are shown in Figures 24 and 25 respectively. Data were coded such that positive z-scores reflect improvement relative to baseline. These figures show within-group improvement for individual patients across: (a) standardized tests of executive functioning; (b) self-rated executive functioning; (c) informant-rated executive functioning; and (d) self-rated mood and sleep quality. Table 16 summarizes the mean composite scores (Section 3.3.1.2.3) for each intervention group at baseline, post-training and follow-up.

Behavioural PLS including both groups did not show a significant relation (permuted p > .3) of pre-training disease severity or mood indices on composite change scores. Paired t-tests were used to quantify within-group change in patients’ mean composite scores (Section 3.3.1.2.3) from baseline to post-training and follow-up, with between-group t-tests to compare composite change scores (Section 3.3.1.2.4) for the GMT and BHW groups at post-training and follow-up.

Within-group analyses showed significant baseline-to-post-training improvement in the GMT group for the executive-attention test composite, \( t(12) = 2.622, p = .022 \), and the quality of life composite, \( t(12) = 2.281, p = .041 \), with marginal improvement in informant-rated executive functioning, \( t(8) = 1.874, p = .098 \). BHW patients showed marginally significant improvement on the quality of life composite, \( t(13) = 2.141, p = .052 \). The BHW group improved on self-reported executive functioning, \( t(13) = 3.908, p = .002 \), but with no significant improvement on the executive-attention composite (p > .3). Change on the executive-attention test composite was greater for GMT compared to BHW patients, \( t(25) = 1.861, p = .037 \).

At follow-up, the GMT group continued to show gains compared to baseline on the executive-attention test composite, \( t(10) = 2.750, p = .020 \), and informant-rated composite, \( t(8) = 3.026, p = .016 \). BHW patients’ mean self-rated executive functioning, \( t(12) = 3.394, p = .005 \), and quality of life, \( t(11) = 2.086, p = .061 \), were greater compared to baseline. Informant-rated executive functioning was also significantly improved in the BHW group at follow-up, \( t(8) = 3.374, p = .010 \), however this was not accompanied by any significant improvement across the executive-attention test composite (p > .1) and was marginally smaller than informant-rated improvement seen in the GMT group, \( t(16) = 1.488, p = .078 \).
Figure 24. Individual differences in composite outcome scores post-training

(a) EF tests

(b) Self-rated EF

(c) Informant-rated EF

(d) Self-rated QoL

EF = executive functioning; QoL = quality of life (mood and sleep quality) measures
Figure 25. Individual differences in composite outcome scores at 6-month follow-up

(a) EF tests

(b) Self-rated EF

(c) Informant-rated EF

(d) Self-rated QoL

EF = executive functioning; QoL = quality of life (mood and sleep quality) measures
Table 16. Composite-scored outcome measures in the patient intervention groups

<table>
<thead>
<tr>
<th></th>
<th>Group mean composite (z) score</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GMT</td>
<td>BHW</td>
<td>GMT</td>
<td>BHW</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Executive-attention tests</td>
<td>Baseline</td>
<td>-0.06</td>
<td>0.60</td>
<td>0.04</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Post-training</td>
<td>0.20</td>
<td>0.50</td>
<td>*</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0.22</td>
<td>0.38</td>
<td>0.20</td>
<td>0.46</td>
</tr>
<tr>
<td>Self-rated executive functioning</td>
<td>Baseline</td>
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<td>0.80</td>
<td>-0.05</td>
<td>0.89</td>
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<td>0.63</td>
<td>0.43</td>
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<td>Follow-up</td>
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<td>0.61</td>
<td>0.76</td>
</tr>
<tr>
<td>Informant-rated executive functioning</td>
<td>Baseline</td>
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<td>0.98</td>
<td>-0.01</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>Post-training</td>
<td>0.23</td>
<td>1.07</td>
<td>0.09</td>
<td>1.01</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>0.56</td>
<td>0.59</td>
<td>±</td>
<td>0.41</td>
</tr>
<tr>
<td>Self-rated quality of life</td>
<td>Baseline</td>
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<td>0.12</td>
<td>0.82</td>
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<td></td>
<td>Post-training</td>
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<td>Follow-up</td>
<td>0.26</td>
<td>0.47</td>
<td>0.62</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Within-group change relative to baseline indicated by boxed values (p < .05) or shaded values (.05 < p < .10). Between-group difference in change relative to baseline indicated by * (p < .05) or ± (.05 < p < .10).

5.6 Intervention effects on neurophysiological measures

5.6.1 Comparison of treatment groups on ERPs

Mean ERP amplitudes for the components examined for intervention effects are summarized by intervention group and test time in Table 17.

Using 2 x 3 x 6 mixed design ANOVAs with Treatment (GMT, BHW), Time (baseline, post-training, follow-up) and ROI (fronto-central, right and left frontal, centro-parietal and left and right parietal) as factors, no changes in mean P3 amplitudes on (correct) SART Go or No-go trials reached significance, either between or across the intervention groups, at post-training or 6-month follow-up (p’s > .1). The 2 x 3 ANOVAs with Treatment (GMT, BHW) and Time (baseline, post-training, follow-up) as factors also did not reach significance for mean error-related (ERN and Pe) amplitudes (p’s > .1).
Table 17. Mean amplitudes for ERPs of interest by ROI, trial type and intervention group at baseline, post-training and 6-month post-training follow-up

<table>
<thead>
<tr>
<th>SART Trial Type</th>
<th>Mean Amplitude (µV)</th>
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<th></th>
<th></th>
<th></th>
<th></th>
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<td></td>
<td></td>
<td>L-Fr</td>
<td>Fr-C</td>
<td>R-Fr</td>
<td>L-Par</td>
<td>C-Par</td>
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<td>Correct Go</td>
<td>GMT</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
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<td>Post-training</td>
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<td>1.02</td>
<td>0.70</td>
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<td></td>
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<td>1.15</td>
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<tr>
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<td>Baseline</td>
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<td>0.98</td>
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<td>Follow-up</td>
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<td>0.84</td>
<td>0.84</td>
<td>1.04</td>
<td>0.43</td>
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<td>Correct No-go (&quot;Stop&quot;)</td>
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<tr>
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<td>2.18</td>
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<td>3.04</td>
<td>3.00</td>
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<td>2.30</td>
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<td>1.40</td>
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<td>Baseline</td>
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<td>3.07</td>
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<td>(Go Correct – No-go Error)</td>
<td>Baseline</td>
<td>-1.89</td>
<td></td>
<td></td>
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<td>0.36</td>
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<td>Post-training</td>
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<td>Follow-up</td>
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<tr>
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<td>BHW</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
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<td></td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
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<td>Post-training</td>
<td>-3.73</td>
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<td></td>
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<tr>
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<td>Follow-up</td>
<td>-1.85</td>
<td></td>
<td></td>
<td></td>
<td>1.15</td>
</tr>
</tbody>
</table>

P3 ROIs: L-Fr = left frontal; Fr-C = fronto-central; R-Fr = right frontal; L-Par = left parietal; C-Par = centro-parietal; R-Par = right parietal

ERN = error-related negativity; Pe = error-related positivity
5.6.2 Relations of ERP change to behaviour change with intervention

Behavioural PLS produced two significant and one marginal LV (Table 18), however inspection of the ERP-behaviour scatter plots revealed two multivariate ERP outliers (Appendix 5). These included a GMT patient who had the greatest increase in ERN amplitude within the GMT group and a BHW patient who had the greatest amplitude decreases in several P3 ROIs within the BHW group (though neither were univariate statistical outliers). These patients were excluded and the analysis re-run, again producing two significant LVs (Table 18).

Table 18. Summary of post-intervention ERP-behavioural PLS analyses

<table>
<thead>
<tr>
<th></th>
<th>First analysis (all data)</th>
<th>Second analysis (2 ERP outliers excluded)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>LV 1</td>
<td>LV 2</td>
</tr>
<tr>
<td>Singular value</td>
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<td>2.2187</td>
</tr>
<tr>
<td>Permuted p</td>
<td>0.006</td>
<td>0.016</td>
</tr>
<tr>
<td>% covariance</td>
<td>30.38</td>
<td>22.88</td>
</tr>
</tbody>
</table>

The first LV (permuted p < .001, accounting for 34% of the cross-block covariance, Figure 26) linked baseline to post-training increases in frontal P3 amplitudes on Go and No-go trials and ERN amplitudes (on No-go error trials) to improved TEA-3, TEA-4 and Tower Test achievement score in GMT patients. Only one measure surpassed threshold for the BHW patients: improved (i.e., reduced) SART omission errors.

The second LV (permuted p < .032, accounting for 23% of the cross-block covariance, Figure 27) linked baseline to post-training increases in parietal P3 amplitudes on Go trials (but reduced No-go parietal P3 amplitudes) to improvement (i.e. reduction) in SART commission error rates and RT variability in the GMT group as well as to “offline” improvement on the TEA-4 in both GMT and BHW groups.
Figure 26. Relation of baseline-to-post-training changes in ERP amplitudes to behavioural changes on cognitive tests in each intervention group (behavioural PLS): LV1

P3 ROIs: L-Fr = left frontal; Fr-C = fronto-central; R-Fr = right frontal; L-Par = left parietal; C-Par = centro-parietal; R-Par = right parietal

All ERPs coded such that greater positive values corresponded to increased amplitudes (i.e. greater positive P3 and Pe amplitudes and greater negative ERN amplitudes)

(r) = test scores reverse-coded such that all positive values correspond to improved test performance
Figure 27. Relation of baseline-to-post-training changes in ERP amplitudes to behavioural changes on cognitive tests in each intervention group (behavioural PLS): LV2

All ERPs coded such that greater positive values corresponded to increased amplitudes (i.e. greater positive P3 and Pe amplitudes and greater negative ERN amplitudes)

(r) = test scores reverse-coded such that all positive values correspond to improved test performance
At the 6-month follow-up, behavioural PLS resulted in one significant LV (permuted p < .001, accounting for 46% of the cross-block covariance, Figure 28). GMT improvement (reduction) in SART commission errors and RT variability associated with increased ERN and/or decreased P3 and Pe amplitudes. By contrast, SART post-error RT slowing was positively related to P3 and Pe amplitude changes. In the BHW group, P3 and Pe amplitude changes were linked to omission error reduction. (As in the post-training analyses, a similar correlation in the GMT group (.362) did not reach significance.) BHW patients’ improvement on the Hotel Test indices at follow-up associated inversely with changes in the P3 and Pe amplitudes but positively with increased ERN amplitude.
Figure 28. Relation of baseline-to-follow-up changes in ERP amplitudes to behavioural changes on cognitive tests in each intervention group (behavioural PLS)

All ERPs coded such that greater positive values corresponded to increased amplitudes (i.e. greater positive P3 and Pe amplitudes and greater negative ERN amplitudes)

(r) = test scores reverse-coded such that all positive values correspond to improved test performance
As all amplitude changes were coded such that positive values indicated increased amplitudes (i.e. more positive P3 and Pe but more negative ERN amplitudes), the ERP-behaviour results at post-training and follow-up suggested an inverse relation between change in the ERN and Pe amplitudes themselves as well as their relation to behavioural change. Scatter plots confirmed an inverse relation of amplitude increases in these ERPs at post-training and follow-up (Figure 29).

Figure 29. Relation of ERN to Pe amplitude changes in MS patients

(a) Baseline to post-training

(b) Baseline to follow-up

![Scatter plots showing the relation of ERN to Pe amplitude changes.](image)

ERPs coded such that greater positive values corresponded to increased amplitudes (i.e. greater positive Pe and greater negative ERN amplitudes)

Scatter plots also indicated dissociative patterns of ERP-behavioural changes between these two components. For example within the GMT group from baseline to post-training, increased Tower Test achievement scores related to increased ERN amplitudes but decreased amplitudes in the Pe window (Figure 30a-b). The same pattern obtained from baseline to follow-up in relation to improvement (decreases) in SART commission error rates (Figure 30c-d). Although in the PLS results the BSR for Pe amplitude change suggested a positive relation to omission error improvement (in BHW patients) at follow-up, scatter plots showed a very weak relation in both groups (Figure 31). The sole positive relation of Pe change to behaviour occurred with increased SART post-error slowing in the GMT (but not BHW) group (Figure 31b,d).
Figure 30. Example scatter plots relating change in behaviour (test scores) to ERN and Pe amplitude changes in GMT patients at post-training and follow-up

(a) ERN – Tower Achievement, post-training

(b) Pe – Tower Achievement, post-training

(c) ERN – SART Commission Errors, follow-up

(d) Pe – SART Commission Errors, follow-up

ERPs coded such that greater positive values corresponded to increased amplitudes (i.e. greater positive Pe and greater negative ERN amplitudes)
Figure 31. Example scatter plots of Pe amplitude change in relation to SART behaviour change in GMT and BHW patients at follow-up

(a) Pe – SART Omission Errors, GMT group
(b) Pe – SART Post-Error RT Slowing, GMT group

(c) Pe – SART Omission Errors, BHW group
(d) Pe – SART Post-Error RT Slowing, BHW group

ERPs coded such that greater positive values corresponded to increased amplitudes (i.e. greater positive Pe and greater negative ERN amplitudes)

To further investigate the unexpected dissociation of ERN and Pe amplitude changes in the behavioural PLS analyses, patients’ waveforms across the repeated testing sessions were
examined. As seen in patients’ ERP results at baseline (Chapter 4) and in Figure 32, patients’ response-locked waveforms at post-training ($t(23) = -3.376, p = .003$) and follow-up ($t(23) = -2.632, p = .015$) continued to feature a clear, reliable ERN. Patients’ change values for this component indicated small shifts in its amplitude that were, in the behavioural PLS analyses reported above, associated to behavioural change in the expected direction.

**Figure 32.** MS patients’ response-locked ERP waveforms in the fronto-central ERN ROI

(a) At post-training

![Graph of ERP waveforms at post-training](image)

(b) At the 6-month follow-up

![Graph of ERP waveforms at follow-up](image)
By contrast, there remained no significant subsequent positive peak in MS patients’ error-locked waveforms, i.e., no Pe, at either post-training ($t(23) = .984, p = .336$) or follow-up ($t(23) = 1.533, p = .139$). Despite small shifts in amplitudes across patients’ repeat testing, the Pe was not a reliable component of patients’ waveforms (Figure 33). Implications for interpreting the relation of amplitude shifts in the “Pe” window to behaviour change are discussed in the next chapter.

**Figure 33.** MS patients’ response-locked ERP waveforms in the centro-parietal Pe ROI

(a) At post-training

(b) At the 6-month follow-up
Chapter 6
Discussion

Prior to intervention, this sample of MS patients presented with behavioural deficits in processing speed and several aspects of executive functioning. These related to behavioural indices of disease severity and DWMI progression as well as neural activity (mean ERP amplitudes) related to attentional control and self-monitoring. Evidence from objective, standardized cognitive tests was complemented by findings of functional impairment including subjective and observed daily functional executive-attention difficulties. Patients also reported mood and sleep disturbance; these related to patients’ subjective cognitive complaints but did not account for objective indicators of cognitive impairment. Together these findings are consistent with but also address some gaps in the existing literature regarding the impact of MS on neurocognitive functioning in the executive domain.

Results from the rehabilitation trial showed significant general effects of both GMT and BHW on several measures, but with evidence for additional, specific effects of GMT in the reduction of executive and self-regulatory impairment for patients with MS. Greater improvement compared to the active control (BHW) condition was seen across a multi-level outcome battery including tests of executive-attentional processes (with linkage to neurophysiological markers), functional task performance and observable functioning in daily life activities. As discussed in greater detail below, while a larger-scale study may be needed to address some of the limitations in this study, the findings reported here offer a novel contribution to the literatures on cognitive rehabilitation for people with MS as well as the neural, cognitive and functional effects of GMT.

6.1 Combined neurophysiological and behavioural characterization of executive dysfunction in MS

Prior research in MS patients has shown executive functioning to be one of the most commonly affected cognitive domains (Beatty, 1993; Benedict, Cookfair, et al., 2006; Birnboim & Miller, 2004b; Bobholz & Rao, 2003; Chiaravalloti & DeLuca, 2008; Crivelli, et al., 2012; Huijbregts, et al., 2006; Leocani, et al., 2000; Matotek, et al., 2001; Rao, 1995; Rendell, et al., 2007). Using a selection of measures, authors have variously described impairments in working memory, cognitive flexibility, conceptual-abstract reasoning, planning, strategy application, prospective
memory and the executive control of attention (e.g., sustained attention, attentional shifting and interference suppression). Several have also described memory deficits, most consistently in aspects of learning and memory that are most reliant on attention and executive functions such as encoding and retrieval strategies. Verbal fluency deficits may also reflect an influence of reduced executive control of attention and retrieval (Matotek, et al., 2001; Troyer, et al., 1997).

In addition to any component cognitive deficits, reduced information processing speed appears to be a highly common, global consequence of demyelination and DWMI in MS (Benedict, Cookfair, et al., 2006; Chiaravalloti & DeLuca, 2008; Rao, St. Aubin-Faubert, & Leo, 1989).

Few have attempted to comparatively determine, within the same patient sample, the executive processes most sensitive to progressive DWMI in MS. Results obtained with this study’s unusually large battery of executive measures begin to address this question in patients spanning the RRMS-SPMS disease severity spectrum.

As a group (in comparison to neurologically healthy controls), MS patients were significantly impaired on indices of processing speed (time to complete Trails A), attentional switching (Trails B-A time difference, TEA-4) and self-monitoring including sustained attention to the task goal (Hotel Test number of tasks attempted), prospective memory (Hotel Test garage door deviation score) and sustained attention to task rules (Tower Test). While these findings alone indicate a pattern of cognitive slowing and executive dysfunction, it was interesting that significant group differences did not emerge on more measures considering that patients were referred or recruited specifically for visible or suspected executive-attentional impairment (Chapter 3). Group findings did indicate significant self- and informant-rated impairment in everyday executive functioning, with patients showing good insight into their level of cognitive disability. Together with the sensitivity of the Hotel Test (which, of all cognitive measures used most closely simulates “real-life” executive challenges) these findings highlight the clinical problem of fully capturing executive deficits on process-oriented tests (even with a broad selection of well-validated measures) and the need to include functionally-oriented assessment tools (Burgess, et al., 2006).

Within the patient group, the cognitive test battery was sensitive to disease severity as indicated by disease duration (particularly in the SPMS subgroup) and neurological disability (EDSS), which reflect the extent of disease progression and accumulated DMWI (Caramanos, et al., 2012;
Ge, et al., 2000). Using these indices, patients’ disease severity associated with reduced information processing and psychomotor speed (e.g., SDMT oral and written, Trails A completion time and PASAT), consistent with prior research relating processing speed to white matter integrity in populations including MS patients (Demaree, DeLuca, Gaudino, & Diamond, 1999; Rao, St. Aubin-Faubert, et al., 1989; Turken, et al., 2008). Patients’ estimated intelligence (Shipley vocabulary) and visuo-spatial perception (JLO) were not affected however measures involving visual scanning (which requires visuo-spatial shifts in attention, e.g. SDMT, Trails A and B) were sensitive to disease severity (though the relative effects of scanning and processing speed deficits could not be determined due to overlap in the measures used).

Simple span of attention / working memory (Digit Span forward) and low-demand working memory manipulation (Digit Span backward) were not significantly linked to disease severity in this patient sample (indeed, as a group, patients marginally outperformed controls on the latter). However, tasks requiring more extensive manipulation and updating of working memory content (PASAT, TEA-5, Tower Test) were sensitive to disease severity. Bootstrap ratios suggested a correspondence between increased working memory load and impairment, e.g. greater for PASAT 2” compared to 3” (corresponding to an increased rate of stimulus presentation) and for TEA-5 compared to TEA-3 (corresponding to a shift from simple counting in TEA-3 to counting with directional reversal in TEA-5). The impact of disease severity on a measure of planning and action sequencing (Tower Test) may reflect, at least in part, a similar working memory deficit limiting patients’ ability to visualize the steps or subgoals needed to get to the final solution.

Patients performed at ceiling on a simple vigilance task (TEA-2) but were impaired as a function of disease severity across several measures that required sustained, active control of attention (SART, PASAT, TEA-3 and TEA-5, Hotel Test). This was reflected in both accuracy (e.g., SART commission and omission errors) and response stability (e.g. SART reaction time variability), convergent with prior findings relating to DMWI in TBI (Robertson, et al., 1997; Stuss, et al., 2003). MS patients’ ability to selectively attend to task-relevant information while suppressing cognitive interference was impaired whether they were required to attend to constant (e.g., TEA-3) or variable (e.g., PASAT) stimuli. Patients likewise showed behavioural evidence of difficulty sustaining attention to task goals (e.g., “withhold to ‘3’” on the SART, “sample all tasks” on the Hotel Test) in the face of interference from competing response schema (e.g., “press to digits [other than ‘3’]” on the SART) or stimulus-bound response options (e.g., getting
drawn into an individual task on the Hotel). Failure to sustain attention to task parameters was also evident with more instances of rule violations (Trails, Tower Test) in patients with more severe disease. Deficits in patients’ capacity to switch or divide attention (cognitive flexibility) included shifting between stimulus sets (e.g., between numbers and letters on Trails B) or response sets (e.g., between counting up and counting down on the TEA-4 and TEA-5) and dividing attention (e.g. adding the immediately previous stimulus pair while continuing to register the next items in the continual stimulus stream on the PASAT).

Together, behavioural results (prior to intervention) indicated reduced processing speed and inefficient recruitment of executive networks attributable to the impact of DWMI on neural connectivity in MS (Dineen, et al., 2009; Honig, et al., 1992; Lazoner, et al., 2004; Leocani, et al., 2000; Loitfelder, et al., 2012; Mainero, et al., 2006; Piras, et al., 2003). Impairment as a function of disease severity was seen in patients’ executive control of attention including capacities for sustained attention, selective attention (with interference suppression) and dividing/switching attention. Executive control of working memory, i.e. manipulation and updating of online mental representations, was also reliably and inversely related to indices of disease progression. By contrast, simple attention span, vigilance (on the TEA-2 “watch-keeping” paradigm) and low-demand working memory (in low interference contexts) remained relatively preserved, as did general intellectual ability.

Note that in the current study, simple “vigilance” (i.e., maintaining count of stimuli against a low-interference background) was distinguished from “sustained / vigilant attention” (i.e. active maintenance of response readiness over time, see Manly & Robertson, 1997; Robertson & Garavan, 2004). Such “response readiness” can be assessed through either the timing or accuracy of a subject’s response to the target. Paradigms emphasizing response time (Crivelli, et al., 2012; Urbanek, et al., 2010) may not adequately control for psychomotor speed deficits in MS. However, on the SART the primary indicator of response readiness is the rate of commission errors on No-go trials where the demand is for no motor response. Using this measure, results were consistent with prior studies (Crivelli, et al., 2012; Urbanek, et al., 2010) showing impaired sustained attention in MS.

While the test battery did not include full assessment of memory abilities, indices of prospective memory and strategic memory retrieval were impaired in MS patients, consistent with prior
research linking these “memory” problems to the influence of executive dysfunction (Marsh & Hicks, 1998; Matotek, et al., 2001; Rendell, et al., 2007). Patients’ failures to maintain goal-directed behaviour (e.g. omitting some Hotel tasks) and respect task parameters (e.g. making rule violations) were also attributable to a deficit in self-regulatory attention moreso than memory, as probing revealed intact knowledge of what they were “supposed” to do – illustrating the dissociation of intention from action characteristic of executive dysfunction and goal neglect (Duncan, et al., 1996; Kane & Engle, 2002; Shallice & Burgess, 1991).

Given the small sample of patients, the current findings offer a tentative fractionation of the executive impact of MS. Future research in a larger sample with factor analytic methodology and, ideally, relations to more direct measures of disease progression (e.g., volumetric MRI, MRS) would be recommended. Developments in computer-based (Connors, 2004; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Maruff, et al., 2009; Troyer, et al., 2012) and particularly online (Hampshire, Highfield, Parkin, & Owen, 2012) assessment tools could make this line of research more feasible in the near future by facilitating participation of patients with mobility limitations and the administration of larger group studies. A well-validated and accessible computerized battery, assembled from measures sensitive to impairment and disease progression, could further be useful to facilitate screening for cognitive issues that may otherwise be missed and unaddressed in MS patients’ routine medical care.

In addition to cognitive deficits and consistent with prior research (Chiaravalloti & DeLuca, 2008; Ghaffar & Feinstein, 2007; Haussleiter, et al., 2009; Janardhan & Bakshi, 2002), MS patients in the current study were also prone to mood disturbance, endorsing feelings of depression and anxiety significantly greater than those reported by neurologically healthy controls. Self-reported sleep quality was also marginally poorer.

Consistent with prior research (Benito-León, et al., 2002), depressive-anxious mood disturbance related directly to indices of disease severity, particularly in SPMS patients. Patients with greater disease severity additionally endorsed a greater level of anger. This aspect of mood disturbance has been less studied in MS, though could relate to disrupted limbic connectivity and emotional regulation (Nocentini, et al., 2009) and/or disease-related stress or frustration (Mitchell, et al., 2010). Severity of self-reported fatigue (though not sleep quality) was also correlated with disease progression. Patients’ mood disturbance related to their subjective evaluation of
executive deficits, though the directionality (i.e., whether the mood disturbance is reactive to or causative of perceived cognitive impairment) cannot be determined from these data. Mood disturbance also related to informant-rated cognitive functioning but did not account for patients’ performance on standardized tests, suggesting that mood disturbance and cognitive impairment exist as separate if partially overlapping issues in patients with MS.

Replicating prior SART research, neurologically healthy controls with faster mean RT and greater RT variability made significantly more commission (No-go) as well as omission (Go) errors, indicating a greater tendency for lapsed attention (Garavan, et al., 2002; Manly, et al., 1999; Stuss, et al., 2003). In comparison to some previous SART studies, controls in this study showed minimal PES (in fact significantly less so than the MS patients) but a higher rate of commission errors (Manly, et al., 1999; Robertson, et al., 1997). Controls’ poorer performance in the current study may reflect an effect of doing the task with simultaneous EEG recording. Previous EEG SART studies have produced comparable error rates (Datta, et al., 2007; Zordan, et al., 2008) but did not report on PES. In the one available (behavioural) study that reported both error rates and PES in controls and patients with DWMI (due to TBI), reduced PES in patients occurred together with more commission errors (Robertson, et al., 1997). In the current study, the MS patient group’s greater PES, an indicator of greater response caution (Dutilh, et al., 2012), may have enabled their unexpectedly similar (i.e., preserved) averaged SART accuracy relative to controls. PES and commission error rates were inversely related within the patient group, with no significant relation in the control group.

Consistent with prior research and slower global processing speed (Aminoff & Goodin, 2001; Honig, et al., 1992; Magnano, et al., 2006; Triantafyllou, et al., 1992; Vázquez-Marrufo, et al., 2008; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Bramham, et al., 2010), latencies of all stimulus-linked ERP components including the P3 were slowed in MS patients. Of greater interest for the current study, ERP (P3, ERN and Pe) mean amplitudes were analyzed as indices of the intensity, rather than timing (Kok, 2001; Luck, 2005), of their associated executive control processes.

As hypothesized, P3 amplitudes were greater on (correct) No-go compared to Go trials in controls as well as patients, consistent with attentional engagement and possibly concomitant heightening of arousal (Braver, et al., 2001; MacDonald, et al., 2000; Nieuwenhuis, et al., 2005).
These amplitude differences were most robust across the parietal ROIs (in both controls and patients), with smaller differences in the right and central frontal (controls) or left and central frontal (patients) ROIs.

Controls’ P3 topography featured the typical central No-go maximal amplitude, with more posterior (in the current study, bilateral rather than central) Go-linked peaks (Garavan, et al., 2002; Key, et al., 2005; Zordan, et al., 2008). As hypothesized, P3 amplitudes were attenuated in MS patients relative to controls. This effect was strongest on No-go trials and over right hemispheric ROIs, resulting in a more posterior (parietal as opposed to central) and left-lateralized No-go P3 maxima. Though ERP source analysis was not attempted here, these findings in MS patients suggest reduced or poorly coordinated activity in right frontal and parietal nodes of the sustained attention network previously implicated in SART performance (Garavan, et al., 2002; Mottaghy, et al., 2006; O’Connor, et al., 2011; Pardo, et al., 1991; Posner & Peterson, 1990; Richard, et al., 2010; Sturm, et al., 1999). Topography of the Go-linked P3 was similar in patient and control groups, though featured a slight anterior shift in progressive patients which may indicate cognitive inefficiency (see below). Within the MS patient group greater disease severity associated with P3 amplitude reductions on Go as well as No-go trials, in either case with a gradient from right through left parietal ROIs and from the fronto-central to lateral frontal ROIs in patients with more advanced disease. These results dovetail with prior evidence of P3 amplitude attenuation (over parietal and, to a lesser extent, frontal sites) with disease progression / severity in MS (Ellger, et al., 2002; Honig, et al., 1992; Kiiski, Reilly, et al., 2011; Piras, et al., 2003; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Hutchinson, et al., 2010) though none have described the partial laterality effect seen here.

In addition to task demand (i.e. SART trial type), P3 amplitudes were also reflective of task accuracy in controls and patients, with greater amplitudes on successfully inhibited No-go trials (stops) compared to commission errors across all parietal ROIs in both groups. P3 amplitudes also appeared greater on accurate compared to omitted Go trials, though the difference approached statistical significance only in the patient group and only in the fronto-central ROI. This might indicate some degree of DWMI-induced cognitive inefficiency in MS patients, with attentional resources linked to performance even in the relatively low-demand SART Go trials, similar to findings in TBI (Richard, Levine, O’ Connor, & Robertson, (in preparation); Stuss, et al., 1989; Turner & Levine, 2008).
Partial support was obtained for the hypothesis that individual differences in mean P3 amplitudes would be predictive of successful task behaviour, notably with a different pattern in controls compared to patients. In controls, better SART performance (lower commission error rates as well as slower and less variable response timing) was seen in those with smaller P3 amplitudes, particularly in parietal ROIs and on Go trials. In patients, neither Go- nor No-go-linked P3 amplitudes related to commission error rates, but patients with greater frontal and parietal P3 amplitudes made fewer omission errors and showed better response stability. In contrast to controls, better performance in these patients associated with faster mean RT – which, relative to the patient group, suggests comparatively less DWMI and global slowing. Also in patients – more reliably than in controls – greater P3 amplitudes during the SART associated with less cognitive impairment on measures of processing speed, attention control and performance monitoring (e.g., SDMT, PASAT, Trails (B-A time, total errors), TEA-3, Tower move accuracy and rule violations) completed “offline” in the broader neuropsychological battery. Thus, in addition to replicating prior studies showing attenuated P3 amplitudes with MS disease progression (as described above), this study provided novel evidence of a link to behaviour on the EEG task itself (SART indices) with apparent generalization to patients’ broader performance on a battery of cognitive tests involving attentional control.

Results also partially supported the hypothesis that P3 amplitude changes from pre-to-post commission errors would relate to behavioural correction. At the group level, P3 amplitudes on Go trials preceding and following No-go trials did not differ significantly and therefore could not be said to index differences in attentional allocation (Datta, et al., 2007; Smallwood, et al., 2008). However, in controls, amplitude increases – most strongly over left and central parietal sites – associated with increased RT slowing following commission errors. Consistent with controls’ overall SART behaviour patterns as discussed above, this neurocognitive post-error change did not significantly impact on other SART behaviour variables. In the MS patient group, the multivariate association to PES did not reach significance though a link to overall slower mean RT and fewer commission errors suggested increased or re-engaged self-monitoring and controlled, attentive responding (Dutilh, et al., 2012; Garavan, et al., 2002; Manly, et al., 1999; O’Connor, et al., 2011; Patel & Azzam, 2005; Robertson, et al., 1997). However, this occurred together with a greater number of omission errors suggesting a behavioural trade-off. That is, patients who slowed responses to reduce their likelihood of failed inhibitions on SART No-go
trials had a greater incidence of missing responses on Go trials. While amplitudes within the ROIs cannot be taken as direct measures of activity in underlying cortex with any anatomical specificity, the combination of amplitude increases and decreases with behavioural trade-offs seen in MS patients but not controls suggests reduced interregional coordination consistent with DWMI (Bonnet, et al., 2010; Segalowitz, et al., 1997). Nonetheless, these findings highlight the role of neurocognitive self-monitoring and adjustment mechanisms to the allocation of attention, indexed here by P3 amplitude, and the maintenance of goal-directed behaviour (“don’t press to ‘3’”) in MS patients. Results also demonstrate disease-related variability across MS patients in their residual capacity for such executive control.

Latencies in the No-go-error-linked ERP components (ERN and Pe) did not appear visibly affected in MS. However, disease severity affected the amplitude of the Pe, to the extent that it was not reliable (i.e., not significantly greater on No-go error compared to correct Go trials) in the MS group-averaged waveform. ERN amplitudes appeared relatively resistant to disease severity however were sensitive to task performance with similar ERN-behaviour patterns in control and patients. Greater (i.e., more negative) ERN amplitudes (in response to having made a commission error on the SART) associated with fewer omission and commission errors as well as more stable responding in patients and controls. While this is the first investigation of error-related ERPs during the SART specifically, results are consistent with the centrality of resolving competing response schema (Van Veen & Carter, 2002a; Yeung, et al., 2004) in this paradigm (i.e., “press to digits other than 3” versus “withhold to 3”) and with other studies linking ERN amplitude to response accuracy (Hajcak, et al., 2003; Westlye, et al., 2009).

Though previously unstudied in MS patients, these results together with the behavioural relation of PES to SART accuracy in patients but not controls (described above) highlight the role of performance monitoring and behavioural adjustment to maintain task performance as also seen in neurologically healthy individuals (Debener, et al., 2005; Gehring, et al., 1993). While ERN amplitude and latency may not be sensitive to the gross indicators of MS disease progression used in the current study, its amplitude was sensitive to task-based behaviour and also appeared to reflect a performance monitoring capacity that, as hypothesized, seemed to generalize to behaviour across tasks. Future research may be indicated to explore the relation of more direct indicators of cingulate and regional atrophy to ERN amplitude and ERN-behaviour correlations in MS patients.
This study’s behavioural and neurophysiological evidence for slowed processing and impaired executive functioning in MS is not entirely new (Benedict, Cookfair, et al., 2006; Chiaravalloti & DeLuca, 2008; Loitfelder, et al., 2012; Magnano, et al., 2006; Piras, et al., 2003; Whelan, Lonergan, Kiiski, Nolan, Kinsella, Hutchinson, et al., 2010). However, few have assessed multiple component aspects of executive functioning within the same patients and across a range of disease severity to better clarify the nature of the “executive” deficit in MS. This is also, to my knowledge, the first study to investigate the impact of MS on error-related ERPs and their behavioural correlates. Also, while P3 changes in MS had been previously documented, this study advances knowledge of their direct relation to patients’ task performance and broader neuropsychological functioning. For example, MS patients with reduced P3 amplitudes showed less response accuracy and greater response variability during the SART, which parallels findings in TBI (Segalowitz, et al., 1997) and also appeared to reflect an attentional control capacity that generalized across tasks.

The combined ERP (P3, ERN) and behavioural results in this sample of MS patients prior to intervention indicated deficits in executive functioning related to inefficient attentional control. They also suggest that patients may support task performance with a greater emphasis on active performance monitoring to implement behavioural adjustment strategies (e.g., PES). GMT strategies are aimed precisely at enhancing these aspects of self-regulatory control. By training patients to routinely “stop” and consciously take time to reorient their attention, revisit their current goal(s) and break larger goals into more manageable subtasks, GMT may also address the processing speed deficit that accompanies DWMI in MS (Demaree, et al., 1999).

### 6.2 Rehabilitation of executive dysfunction in MS

While results from Study 1 provided some novel contributions to the MS literature, this characterization of baseline functioning was mainly done as a step toward the primary aim of this dissertation: to validate Goal Management Training as a cognitive rehabilitation approach for patients with MS. To satisfy requirements for Class I evidence (Cicerone, et al., 2000; Woolf, 1992) and control for non-specific ("placebo") treatment and test practice effects, GMT was compared to an active psycho-educational control group (the Brain Health Workshop) equated for time spent in group and individual activities and trainer contact.
Both the GMT and BHW programs were well-received by patients, with good attendance in the group sessions and all missed sessions made up individually such that all patients completed their assigned training program. Decreases in self-reported cognitive-executive dysfunction (e.g., absentmindedness, disinhibition, forgetfulness) were seen in both groups with, as predicted, no significant statistical interactions favouring one group over the other. Effect sizes were generally in the small-to-moderate range (Cohen, 1988) and, interestingly, somewhat larger in the BHW group. Self-reported mood and sleep disturbance also decreased with intervention, again as predicted with no statistically significant group differences. Effect sizes were in the small-to-moderate range overall though somewhat larger for the GMT group particularly in reduced reported fatigue, anger/frustration and depressive mood. On most of these self-report measures, within-group effect sizes were similar at post-training and 6-month follow-up, indicating maintenance of patients’ self-perceived benefit.

On cognitive tests sensitive to executive-attentional processes, the hypothesized statistical interaction effects showing better outcomes for patients completing GMT compared to BHW were seen only for the TEA-5. Examination of means differences and effect sizes within each intervention group indicated post-training improvement on the TEA-5 only in the GMT group. This was largely attenuated at the 6-month follow-up, however by that time the BHW group showed a decrease in TEA-5 scores relative to baseline. As an ecologically valid measure (Higginson, Arnett, & Voss, 2000; Robertson, et al., 1996a) of mindful attentional self-regulation (Zylowska, et al., 2008) the TEA-5 thus appeared to be the cognitive test most sensitive to specific effects of GMT. A similar pattern of improvement in the GMT group and decline in the BHW group was visible in the means differences and effect sizes for SART post-error RT slowing at both post-training and follow-up, which suggests improved performance monitoring and adjustment (Dutilh, et al., 2012) and is also consistent with the specific aims of GMT. There was, however, considerable variability in this measure and the omnibus test fell short of statistical significance.

Change was seen in scores on several other cognitive tests in the outcome battery but with statistical significance in the omnibus tests limited to main effects of time (i.e., improvement across groups from baseline to post-training and/or follow-up). Even for these, partial eta squared values indicated considerable unaccounted variance remaining (generally > 80%). Examination of within-group means and standard deviations at each test session indicated a
relatively wide distribution of inter-patient performance on most measures. These may be partly attributed to variability in patients’ degree of response to intervention (further discussed below), however, as similarly wide ranges were seen at baseline, they also likely reflected heterogeneity in the patient sample, e.g. in the extent of disease progression given the inclusion of both RRMS and SPMS patients. This within-group variability together with the small group sizes may have limited statistical power to detect the hypothesized treatment by time interaction effects. Within-group planned contrasts and effect sizes were therefore used to further probe the data with respect to the hypothesized group differences (Levine, et al., 2011; Stubberud, et al., 2013).

On the Hotel Test, a significant or marginal effect of time across groups was seen in both the number of tasks attempted and reduction in the deviation from optimal time-on-task. While the interaction term did not reach statistical significance, effect sizes suggested greater improvement within the GMT relative to BHW group, post-training and even more so at follow-up. A similar pattern obtained in the move-accuracy measure of the Tower Test, again more so at follow-up.

SART omission error rates and rule violations on the Tower Test were reduced as a function of test time with effect sizes suggesting a similar degree of improvement for both groups. Reduction in SART commission error rates did not reach significance in omnibus tests, and though effect sizes suggested greater reduction in the GMT group, the effect (d = .2) was small (Cohen, 1988).

Finally, for three measures with statistically significant (TEA-4) or marginal (SART RT variability, Tower Test achievement score) effects of test time on performance, effect sizes suggested greater improvement in the BHW group particularly at follow-up.

The level of improvement on cognitive outcome measures in the BHW group was unexpected and may represent test practice effects and/or a non-specific benefit to patients from having participated in an engaging and supportive group “intervention” that may also, by providing education about brain function and MS, have served to increased patients’ sense of self-efficacy (Barlow, Wright, Sheasby, Turner, & Hainsworth, 2002; Dixon, Thornton, & Young, 2007). BHW patients’ self-rated improvement in everyday cognitive functioning (at post-training and follow-up) as well as mood and sleep quality would seem consistent with this interpretation. The BHW program was, indeed, modeled on psycho-educational peer support groups that are found in many rehabilitation settings as stand-alone offerings or components of “holistic” programs.
(Cicerone, et al., 2008; Wilson, 2002). As such, the BHW program may be considered a viable form or at least component of neuropsychological intervention in its own right.

Despite BHW patients’ improvements on some cognitive tests, within-group analyses of patients’ standardized (z-scored) change averaged across all cognitive tests showed significant improvement in this composite score from baseline to post-training and baseline to follow-up in the GMT but not BHW group. In conjunction with the omnibus results and effect sizes for the test variables analyzed individually, these cognitive test data provide tentative support for the hypothesis of greater improvement following GMT compared to BHW in this relatively small (and heterogeneous) sample of MS patients. Although the selection of outcome tests had been based on both theoretical and demonstrated sensitivity to the specific effects of GMT, the clearest effects were seen on the TEA-5, Hotel Test and post-error RT slowing on the SART. These measures together suggest improved performance monitoring and control of attention (e.g. flexible, goal-driven attentional switching) in GMT patients to a greater extent than was seen in BHW patients. The observed changes in ERP amplitudes in relation to patients’ behavioural change provided some convergent evidence for this interpretation.

At the group level, the hypothesized interaction effects on mean amplitudes did not reach statistical significance for any of the ERPs of interest (P3, ERN, Pe). These findings are consistent with high test-retest stability inherent in individual subjects’ sensory and cognitive ERPs (Hämmerer, Li, Völkle, Müller, & Lindenberger, 2013; Luck, 2005) and suggest this method may be comparatively less sensitive than fMRI to group-level, averaged changes in neural activation related to cognitive intervention (Chen, et al., 2011; Chiaravalloti, et al., 2012; Filippi, et al., 2012).

ERP amplitudes did, however, appear sensitive to intervention-related behavioural change, which, together with their relative ease of administration even for mobility-restricted MS patients supports their utility (or at least warrants further investigation of their use) in cognitive rehabilitation research (Leocani & Comi, 2000; Magnano, et al., 2006).

Baseline to post-training increases in frontal P3 and ERN amplitudes were significantly related to improvement on measures of attentional control across both groups, with evidence of a broader neuropsychological effect in GMT patients that may indicate better generalization of attentional regulation and performance monitoring across tasks. In the BHW group, this P3-ERN
change pattern significantly associated only with reduced omission errors on the EEG task (i.e., the SART). Whereas this association with SART omission errors did not reach significance in the GMT group, significant positive correlations were seen with the TEA-3, TEA-4 and Tower Test overall achievement score – tests that were completed “offline” and that index patients’ capacities for attentional control (e.g., interference suppression, switching), action planning and self-monitoring. This pattern may represent enhancement of the P3- and ERN-behaviour relations seen in patients (and, for the ERN, neurologically healthy controls) at baseline.

A second significant latent variable related increased parietal Go and decreased parietal (but increased left frontal) No-go P3 amplitudes, also from baseline to post-training, with TEA-4 performance in both groups but additionally with improved response stability and reduced SART commission errors in the GMT group only. These findings are suggestive of possible GMT-related increase in attentional control on two fronts. First, in both neurologically healthy individuals and those with reduced functional connectivity, mean parietal P3 amplitudes on Go trials have been previously linked to greater inter-trial (Datta, et al., 2007; Smallwood, et al., 2008) and inter-individual (Adrover-Roig & Barceló, 2010; Datta, et al., 2007; Segalowitz, et al., 1997) attentional allocation and task performance. The pairing of increased parietal P3 amplitudes on Go trials (which comprise 89% of all SART trials) with improved response stability and inhibitory control on the rare and unpredictably occurring No-go trials suggests a post-training improvement in GMT patients’ capacity for tonic, sustained attention and maintenance of the key task goal (“inhibit response to the number ′3′”) across SART trials – consistent with the hypothesized effect of GMT. Second, though a decrease in parietal No-go P3 amplitudes as contributing to behavioural improvement may seem counterintuitive, particularly considering the link of greater amplitudes to better performance at baseline, they may – together with the patterns seen in the first LV and within-group mean amplitudes – reflect a subtle anterior shift of the No-go P3 in GMT patients, i.e. to a topographical distribution more typical of the No-go P3 in neurologically healthy individuals (Garavan, et al., 2002; Key, et al., 2005; Zordan, et al., 2008). The hypothesized neurocognitive effect of GMT in this study did not include a topographical shift; this may present an interesting direction for future study.

The linkages of SART commission error reduction to reduced RT variability and to increased parietal P3 amplitudes (sustained across Go trials) and ERN amplitudes (in response to making commission errors) combine to suggest a more attentive, controlled approach to task responding...
(Manly, et al., 1999; O'Connor, et al., 2011; Robertson, et al., 1997) in the GMT (moreso than the BHW) group both post-training and at the 6-month follow-up. In addition to consistency with the SART P3 studies described above, these results map onto evidence linking ERN amplitudes to response accuracy in neurologically healthy controls (Hajcak, et al., 2003; Westlye, et al., 2009) and also (in this study) in MS patients. Thus, in addition to Study 1’s novel demonstration of the ERN’s sensitivity to cognitive impairment in MS, Study 2’s findings suggest that changes in the ERN following a targeted executive-attentional rehabilitation program (GMT) are sensitive to behavioural improvement on the EEG task and, perhaps further, to generalized neurocognitive improvement as evidenced by correlations with “offline” cognitive tests including measures of planning, sequencing, attention control and interference suppression.

The observed changes in Pe-behaviour relations are somewhat difficult to interpret. The Pe did not reliably occur in MS patients’ response-locked waveforms at any of the test sessions. While no specific hypotheses regarding relative change in the error-related ERN and Pe were made a priori, their opposing relation to multivariate behavioural change was unexpected. Analyses of the relation between mean amplitudes in the ERN and Pe have been rarely reported (authors have typically reported only their associations to behaviour or task manipulations), but there is some evidence of a direct if small (r’s < .5 across different tasks) correlation (Foti, Kotov, & Hajcak, 2013). As previously described, the ERN and Pe have shown different relations to behavioural indicators of task performance in neurologically healthy individuals (Hajcak, et al., 2003; Hughes & Yeung, 2011; Overbeek, et al., 2005) though these have not typically extended to reports of inverse effects between components. Nonetheless, in the current study increased (i.e., more negative) ERN amplitudes were weakly inversely related to increased (i.e., more positive) “Pe” amplitudes in MS patients over time. Inspection of within-group scatter plots linking change in these two component to change in scores on individual tests indicated that, where ERP-behaviour relations occurred, they involved an association with increased ERN but decreased “Pe” amplitudes (which, given the lack of clear Pe in most patients reflected greater negative difference values in the Pe time window 200-400 ms post-response). The only significant exception was a direct association of increased “Pe” to increased SART post-error

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6 Hereafter amplitudes in this window are referred to as “Pe” since it is not clear from these data that they do in fact reflect typical and/or reliable error-related processing.
slowing in the GMT (but not BHW) group at follow-up. The Pe-PES relation has not been studied in MS but has been shown vulnerable to DWMI in TBI (Larson & Perlstein, 2009). Notably, with the current findings at follow-up, namely the Pe-PES association, the GMT group showed a pattern seen only in neurologically healthy controls in this and previous studies (Hajcak, et al., 2003; Nieuwenhuis, et al., 2001; Wessel, 2011).

In addition to this Pe-behaviour relation at the 6-month follow-up, improvement on several cognitive outcomes measures again related to increased (relative to baseline) ERN amplitudes but decreased P3 amplitudes (now, in all but the right parietal ROI on No-go trials). This ERP change pattern was related to continued improvement (i.e., reduction) of SART RT variability and commission errors in the GMT group, with a new association to performance changes on the Hotel Test indices in the BHW group. (A similar correlation with the number of Hotel tasks attempted did not reach statistical significance in the GMT group owing to the wide confidence interval.) By contrast, but similar to the post-training results, increased P3 amplitudes associated significantly to SART omission error reduction in the BHW group (this correlation also fell short of significance in the GMT group). Although the BSR for the “Pe” in the multivariate analysis suggested a similar positive relation to omission error reduction, scatter plots revealed no such association in either the BHW or GMT group.

The dissociation of ERN and P3 relations to behavioural change at follow-up was unexpected; previous evidence of greater mean amplitudes in the P3, ERN and Pe associating with (different dimensions of) better performance had suggested the hypothesis of a generalized pattern linking increased amplitudes to better behaviour with intervention. In partial support, this pattern was indeed seen for the ERN across test sessions. Relations with P3 amplitude changes were, however, more complex in that they varied across different behavioural measures and ROIs. On the EEG task itself (the SART) results at post-training and follow-up related omission error reduction to increased P3 amplitudes particularly in the frontal ROIs (significant only in the BHW group). These results linking increased ERN and (partially) increased P3 amplitudes to behavioural improvement at follow-up are broadly consistent with the ERP-behavioural relations seen post-training and at baseline (the latter more reliably in MS patient than controls) and may therefore represent persistent intervention-related enhancement of a pre-existing neurocognitive pattern supporting self-monitoring and attentional control in the context of DWMI due to MS.
Interestingly, however, reduced commission errors and RT variability at 6-month-follow-up were more reliably linked to decreased P3 amplitudes, particularly in the parietal ROIs and significant only in the GMT group (in whom this link had been specific to No-go P3 amplitudes at post-training). Rather than the purely “more is better” pattern that was hypothesized, these results raise the possibility of increased efficiency in GMT patients’ control of attentional allocation. Such a result would coincide with mindfulness training effects in neurologically healthy individuals (Brefczynski-Lewis, et al., 2007) as well as the effects of external alerting cues in TBI patients (Richard, et al., 2010). In the only other published study of GMT effects on neural activity, improvement on offline cognitive tests was, in fact, likewise linked with reduced fMRI activation in prefrontal cortex (Chen, et al., 2011) but only in some patients and apparently in relation to pre-training levels of neural activity. These results and those of the present study suggest the intriguing possibility that training in GMT strategy use may help reduce patients’ need for compensatory neural recruitment to maintain task performance (Raja, et al., 2011; Richard, et al., in preparation; Richard, et al., 2010; Turner, et al., 2011). Further study in TBI and MS patients is recommended to clarify the nature of GMT effects on the attentional control network and its component nodes, particularly in relation to individual differences (e.g., severity of pre-training cognitive impairment and/or extent of brain injury or disease progression) and to patients’ cognitive-behavioural outcomes.

If mean amplitudes are reflective of the number of neurons producing the summated activity (Kok, 2001; Luck, 2005), the collection of ERP-behavioural results across both of the current (i.e., baseline and rehabilitation) studies appear consistent with fMRI evidence of compensatory neural activity supporting executive-attentional task performance in MS (Mainero, et al., 2006; Smith, et al., 2009; Staffen, et al., 2002) particularly prior to and immediately following cognitive rehabilitation. The latter ERP-behavioural change patterns (as well as the ERN-behaviour pattern across test times) offer preliminary evidence for the possibility of bolstering such compensatory activity in MS patients through cognitive rehabilitation. Longer-term change patterns (specifically with the P3) suggest the possibility of reducing patients’ reliance on such compensatory activity. Unfortunately, the considerable variability (i.e., wide confidence intervals) in the correlations of behavioural to ERP change limited interpretation for most variables in the cognitive outcome battery. It was also difficult to distinguish GMT-specific
neurocognitive effects from non-specific benefits, considering the occurrence of unexpected ERP-behaviour change in the BHW group.

Nonetheless, particularly at post-training significant ERP-behaviour results spanned multiple measures in the GMT moreso than BHW patients, suggesting improved attention control and performance monitoring on both the EEG task (SART) and “offline” measures which may index immediate GMT-related effects. This in itself is notable for being (1) the second demonstration of possible neural markers of GMT effects (Chen, et al., 2011), (2) the first study to show ERP-behavioural changes over the course of intervention in MS (and possibly in the general cognitive rehabilitation literature as well), particularly (3) in comparison to an active control condition that controls for non-specific or repeat-testing effects. Assuming it is not an artifact of low statistical power, the narrowed range of effects in the GMT group at follow-up may represent some attenuation of treatment effects at least at the neurocognitive level (noting that behavioural effects alone, as reported above, were generally maintained). As the first trial of GMT in a neurodegenerative population, this finding may indicate a need for follow-up or “booster” sessions to maintain maximal effects in patients with progressive disorders. Further investigation in a larger sample of patients could provide the necessary power to more fully investigate the issues of inter-patient variability in treatment response and in long-term treatment effects.

In summary, ERP-behavioural associations suggest a pattern of improved performance monitoring, attention to task, and behavioural self-regulation that was specific to – or at least more reliable within – the GMT group. Effects were strongest at post-training compared to the longer-term follow-up, but some remained there as well and suggested an intriguing combination of increased activity (related to self-monitoring) and increased efficiency (related to attentional allocation). More detailed analysis in a larger-scale study may be needed for more definitive conclusions regarding the neurocognitive effects of GMT. Attention-related neurocognitive effects were not hypothesized for the BHW group and may also merit further study.

Complementing and extending the cognitive test and ERP-behavioural results, measures at the functional level showed greater improvement in the GMT group. Both groups had significant pre-to-post-training gains in goal attainment, but with a significantly greater amount of change in GMT patients. For example, no improvement in goal attainment compared to baseline was seen in 14% of BHW patients whereas all GMT patients improved by at least one scale level. 54% of
GMT patients but only 21% of BHW patients exceeded their target goal, with 23% of GMT patients reaching their “ideal” goals (which no BHW patient achieved). As with self-rated daily executive functioning, informant ratings improved as a main effect of time, i.e. with reduced occurrence of observed executive failures for both GMT and BHW groups. The improvement in the BHW group was unexpected. However, although the predicted treatment by time interactions were not statistically significant, planned within-group contrasts and effect sizes indicated greater gains – both overall and across most DEX subscales – in the GMT relative to BHW group. Similar to the cognitive test results, the small group sizes and high inter-patient variability may have limited statistical power to detect the hypothesized treatment by time interactions on this measure. While replication in a larger sample will (as with the other results) be required for firm conclusions regarding these observable functional effects of GMT, these findings offer tentative evidence of generalized functional improvement following GMT. Critically, informants were kept blind to their loved one’s assigned intervention group and to the hypothesized intervention effects, and their ratings may be considered a more objective indicator of functional improvement than patients’ self-ratings (Burgess, et al., 1998).

Despite significant group-averaged gains (both post-training and at follow-up) on the executive-attention test composite, four of the GMT patients did not improve at post-testing, and two of these patients continued to show no improvement at the 6-month follow-up. The reasons for this response variability unfortunately could not be explained by the available data. Notably, however, patients’ capacity for improvement with GMT did not appear to be limited by disease severity or baseline level of cognitive impairment, supporting the hypothesized applicability of GMT to patients even at a more progressed stage of disease.

Overall, results of this randomized controlled rehabilitation trial converge with GMT studies in other populations and support its extension to people with executive-attentional impairments due to MS. In comparison to previous GMT results in patients with focal lesions in a study with a similar active control group (Levine, et al., 2011), findings on some overlapping measures (the SART and Tower Test) were less robust in this MS study. Stronger effects for GMT and related protocols in other groups (e.g., TBI) on these and other tests of component executive functions (e.g., working memory, attentional switching, interference suppression) have also been reported in studies with “standard care” or minimal intervention conditions (e.g., one 2-hour psycho-educational session) that controlled for test practice effects but with arguably less adequate
control of non-specific treatment or “placebo” effects; two also involved non-neurological populations (Alfonso, et al., 2011; Jackson, et al., 2012; Novakovic-Agopian, et al., 2011). Considering that the current study is the first trial of GMT in an actively neurodegenerative population, results seem encouraging. However, treatment effects, while still significant in MS patients at six months were somewhat less robust than 4-month findings in focal lesion patients (Levine, et al., 2011; Schweizer, et al., 2008) and 6-month findings in spina bifida patients (Stubberud, et al., 2013), which, as noted above, may indicate a need for “booster” sessions to maintain or extend the effectiveness of GMT in patients with progressive brain disorders.

Only one published study has investigated potential biomarkers for GMT (Chen, et al., 2011), specifically for a modified version (Novakovic-Agopian, et al., 2011) that emphasized the practice of mindfulness-based attention and working memory training compared to the most recently published GMT protocol (Levine, et al., 2011). To their credit, this team also assessed outcomes using a multi-level battery including functional measures (the Multiple Errands Test), standardized tests of component executive processes (e.g., working memory) and fMRI activation changes related to goal-directed selective attention and interference suppression. The paradigm was a simple (designed to facilitate performance at ceiling) 1-back working memory task in which chronic-phase TBI patients were instructed to focus on either scenes or faces in displays featuring one of each, with the instruction varied across trials. The main finding was of pre-to-post-training increases in “stimulus-specific” extrastriate regions (i.e., putative “place” or “face” areas) matching the task instructions. These were interpreted as evidence of improved goal-directed attention control, with preferential processing of relevant and suppression of irrelevant stimuli. This was a group-averaged effect (compared to a minimal-treatment period), with no linkage reported to neuropsychological or functional measures.

Considering the differences in imaging modality, scanning task, patient population and intervention, results of the current study complement those of Chen and colleagues (2011) – here describing changes in the sources rather than sites of attention. Though group-averaged changes in the current small study appeared insensitive to intervention effects, the observed ERP-behavioural changes provide tentative convergent evidence for improved goal-driven performance monitoring and behavioural self-regulation following GMT. Source modeling of ERPs was not attempted in this study, however the topographical distribution of the P3, ERN and Pe effects tentatively suggests activity changes in frontal and cingulate regions (Bledowski, et
al., 2004; Herrmann, et al., 2004; Linden, 2005; O’Connell, et al., 2007; Soltani & Knight, 2000; Van Veen & Carter, 2002a) involved in executive and attentional control networks (King, et al., 2010; Knight, Staines, Swick, & Chao, 1999; MacDonald, et al., 2000; Miller & Cohen, 2001; Pessoa, et al., 2003; Silton, et al., 2010).

Though essentially the same intervention used in our group’s most recent GMT study (Levine 2011), the mindfulness training component was made more prominent for this study. In this sense there was similarity to Novakovic-Agiopan, Chen and colleagues’ (2011) program however the current administration also retained the goal-setting, problem-solving and other strategic components of GMT. As a multi-component intervention that expressly does not – unlike computer-training protocols (Filippi, et al., 2012; Mattioli, et al., 2010; Plohmann, et al., 1998; Solari, et al., 2004; Sturm, et al., 1997) – focus training on isolated processes or tasks but instead on learning a generalizable strategy set, the relative contributions of separate GMT aspects to patient outcome results are not readily untangled. One might argue that the mindfulness training alone (i.e., without the concurrent goals- or problem-solving training included in GMT and similar programs) was the key active component, as several studies of stand-alone mindfulness meditation training have reported improved sustained attention, interference suppression and attentional switching albeit in neurologically healthy individuals (Cahn & Polich, 2009; Chambers, et al., 2008; Chiesa, et al., 2011; Jha, et al., 2007; Ortner, et al., 2007; Tang, et al., 2007; Wenk-Sormaz, 2005).

There are several reasons that this seems unlikely. First, prior formats of GMT with less inclusion of mindfulness training have produced results similar to the current study (Grant, et al., 2012; Jackson, et al., 2012; Levine, et al., 2011; Levine, et al., 2007; Schweizer, et al., 2008), albeit with different populations and smaller outcome batteries. Second, even in the dedicated mindfulness studies that prospectively trained meditation-naive participants, nearly all involved much more intensive and prolonged mindfulness practice compared to that included in GMT. To my knowledge, no studies have found comparable executive-attention benefits with less mindfulness practice, which is relevant considering the apparent dose-dependent effects of practice on brain function as well as structure (Brefczynski-Lewis, et al., 2007; Cahn & Polich, 2009; Chiesa, et al., 2011; Lazar, et al., 2005; Lutz, et al., 2004). Third, and perhaps most critically, studies of mindfulness training as a stand-alone intervention have been largely limited to neurologically healthy participants. Despite interest in this line of research (Green & Turner,
the available patient studies appear limited to an uncontrolled trial in ADHD patients (Zylowska, et al., 2008) and a single controlled study of patients with DMWI or focal brain injury secondary to TBI (McMillan, et al., 2002). Though the TBI patients reported subjective improvement, objective test findings were marginal in a pre-post pilot study and were not replicated in a larger RCT (McMillan, et al., 2002).

One possible explanation for McMillan’s (2002) findings is that executive impairment in many patients includes difficulty with independently or spontaneously utilizing or transferring newly learned strategies. The most recent published version of GMT (Levine, et al., 2011), that of the current study and Novakovic-Agiopan, Chen and colleagues’ (2011) modified GMT all present mindfulness with emphasis on its practical application to develop attentional awareness and control in relation to real-life, patient-specific challenges. In this study, mindfulness exercises were kept brief and embedded in the larger set of goal management, problem-solving and self-regulatory strategies, all of which were practiced by patients in guided exercises that approximated different types of real-life situations. GMT’s structured, gradual integration of these strategies into patients’ actual daily activities was designed to explicitly encourage transfer across tasks. Similar embedding of training in the use of external aids (e.g., “to-do” lists) also render these more likely to be transferred and thus effective, in contrast to a program tested in MS patients (ranging in severity) that did not explicitly guide transfer to patients’ daily activities (Lincoln, et al., 2002).

The scope of outcome effects related to GMT in the current study also suggests some advantages over computer-based attention training approaches previously tested in MS (Filippi, et al., 2012; Mattioli, et al., 2010; Plohmann, et al., 1998; Solari, et al., 2004). First, the current study demonstrated effects across several process-oriented tests that were not simply variants of training activities, a weakness common in the computerized retraining literature (O’Connell & Robertson, 2011; Park & Ingles, 2001). This study also showed evidence of generalization to real-life, functional activities. This included improvement in patient-specific goals (measured with GAS), seen – critically – not just on the goal used to practice GMT strategies but the untrained goal as well, with no measurable difference between the two. Convergent evidence was provided by improved behavioural ratings from patients’ informants, who were selected to be very familiar with their usual (baseline) functioning and who were blind to the intervention program assignment and expected results. Notably, in contrast to computerized-retraining studies
with a wait-list control, GMT-linked improvements in the current study were relative to an active comparison program (BHW) providing more stringent control for non-specific treatment and re-testing effects.

6.3 Conclusions

Despite the availability of a good and continually expanding number of process-oriented tests of executive functioning and attention, there remains inherent difficulty in fully capturing an individual’s executive or self-regulatory functioning on the basis of such tests alone (Levine, et al., 2002; Lezak, et al., 2004; Wilson, 2008). Results from the current study provide further illustration of the utility of a multi-level battery when evaluating executive-attentional impairment in MS. In this study, process-oriented cognitive tests described a pattern of deficits in global information processing speed, executive control of attention (sustained, selective, divided/switching) and interference suppression, working memory manipulation and updating, prospective memory and strategic word retrieval that differentiated patients from neurologically healthy controls and/or related monotonically to indices of disease severity. Sensitivity was seen for all indices of the Hotel Test (Manly, et al., 2002), a simulated work environment requiring multi-tasking and goal maintenance similar to real-life situations in which this study’s MS patients described daily difficulties. Whereas a significant multivariate correlation indicated that controls’ cognitive test scores were predictive of their self-rated everyday executive functioning, this was not the case in MS patients. Further, informant ratings provided statistically independent data for all participants. Measures simulating or directly assessing real-life executive functioning thereby added to the data captured by process-specific tests. Results also highlighted the additional importance, with MS patients, of assessing mood disturbance as a separate but potentially influential area of functional impairment.

From this, it can be argued that evaluation of rehabilitation programs targeting self-regulatory control should include – and possibly even emphasize – outcome assessment at the functional level. Meaningful change in the executive domain, perhaps to a greater extent than other targets of cognitive rehabilitation, may not be fully captured by process-based cognitive tests. Failure to provide evidence of meaningful change in patients’ daily activities remains one of the greatest weaknesses in much cognitive rehabilitation research, particularly studies of computerized cognitive re-training. Process-oriented measures, particularly when coupled with neuroimaging
methodologies, may be highly useful to index change and are necessary to address questions about possible mechanisms of change (i.e., about “how” an intervention works). However, these cannot be assumed to fully determine “whether” an intervention will result in improvement that will prove meaningful to the patient’s everyday functioning.

The multi-level outcome battery used in the current study suggested meaningful change at the level of everyday functioning following GMT more so than a psycho-educational program (BHW). As a “top-down” approach – teaching a general strategy to be applied across specific functional tasks – GMT is designed to be effective at the functional outcome level. Results of this and prior studies (Grant, et al., 2012; Levine, Dawson, et al., 2000; Levine, et al., 2007; Miotto, et al., 2009; Novakovic-Agopian, et al., 2011; Schweizer, et al., 2008; Stubberud, et al., 2013, in preparation; van Hooren, et al., 2007) support this conclusion across functional outcome measures including patient-specific goals (e.g. meal preparation), simulated real-life tasks, functional status (e.g., return to work) and self- and/or informant-rated everyday executive functioning. In the current study, some of the strongest evidence favouring GMT compared to BHW emerged on measures most closely relatable to patients’ real-life functioning including an ecologically valid (Higginson, et al., 2000; Robertson, et al., 1996a) measure of attentional self-regulation (TEA-5), a simulated multi-tasking work situation (Hotel Test), patient-centered occupational activities (Goal Attainment Scaling) and informant-rated executive functioning as evident in everyday activities (DEX other). Results on these measures together with increased SART post-error slowing and with ERP-behavioural changes suggest improved performance monitoring and executive control of attention (e.g. flexible, goal-driven attentional switching) as mechanisms of improved behavioural self-regulation in patients completing GMT.

This study is a novel addition particularly to the MS cognitive rehabilitation literature as, to my knowledge, the first to demonstrate improvement in executive-attentional functioning in the context of a randomized trial with an active control condition. Studies comparing an active treatment to a passive (e.g., wait-list) control condition tend to overestimate the resulting “treatment” effects by failing to control for non-specific or placebo effects (Park & Ingles, 2001; Rohling, et al., 2009). In the current study, gains were seen in the control (BHW) group that may have reflected test practice and/or non-specific (i.e., not specifically linked to a targeted cognitive domain) effects, highlighting the importance of including an active control against which to evaluate one’s treatment program. That the GMT group showed gains beyond those
seen in the BHW group arguably provides a higher standard of evidence compared to interventions tested against passive (e.g., standard care or wait-list) control conditions (Filippi, et al., 2012; Mattioli, et al., 2010). One may in turn have greater confidence in drawing conclusions about the apparent effectiveness of GMT as an intervention for executive-attentional impairment in MS, though replication of these results in a larger sample is recommended to address this small study’s statistical limitations (discussed further below).

Notably, positive outcomes with intervention were seen not only in RRMS but also SPMS patients, indeed with no measurable negative impact of disease severity on capacity for improvement. As described earlier, most studies attempting rehabilitation of executive-attentional functions in MS patients have involved computer-based training protocols and have limited participation to patients with RRMS and relatively less advanced levels of disability (e.g., EDSS < 4) (Filippi, et al., 2012; Mattioli, et al., 2010). While reasons for this selectivity were not provided, they may have included practical considerations (e.g. working around mobility impairments that are more likely in SPMS patients) or the assumption that patients with greater disability were less likely to benefit from treatment.

To the extent that computer-based drill-type training protocols are oriented toward restoration of damaged neural networks via repetitive recruitment, limitation to patients with relatively less accumulated DWMI may in fact be advisable to increase likelihood of having sufficient residual tissue in the affected networks to build upon (Cifelli & Matthews, 2002; Kolb, 2004; Robertson & Murre, 1999; Tomassini, et al., 2012). O’Connell and Robertson (2011) have suggested that inclusion of patients with greater injury (usually in studies focused on TBI) may in fact partly explain the dearth of reliable effects from the computerized attention training literature (Park, et al., 1999; Ponsford & Willmott, 2004).

If such training protocols were able to target and strengthen damaged networks, theoretically this is most plausible in individuals with less baseline damage or injury – i.e. with a greater reserve of healthy residual tissue (Robertson & Murre, 1999). Evidence consistent with strengthening in executive-attention networks should include (1) improvement on untrained tasks previously associated with functioning in the target network, and/or (2) neuroimaging findings relating to changes in network activity levels and/or associations to behaviour. The limited number of executive-attention retraining studies that have, in comparison to a valid control condition,
demonstrated such evidence of network recruitment and functional improvement have, to my knowledge, involved either neurologically healthy individuals (Dahlin, et al., 2008; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Persson & Reuter-Lorenz, 2008) or populations with comparatively mild brain disorders, such as ADHD, in the absence of acquired brain injury (Klingberg, et al., 2005). Even for what may be the best-validated of available computer-based approaches (Klingberg, et al., 2005), studies with adequate controls in acquired brain injury populations is lacking and reported effects on daily activities have been limited to patient self-report measures (Johansson & Tornmalm, 2012; Westerberg, et al., 2007).

Being a strategy-focused protocol would not preclude GMT from stimulating and strengthening damaged executive-attentional control circuitry, for example through regular engagement of the attentional control network in the mindfulness exercises (Chen, et al., 2011). Findings from the current study are consistent with this, with ERP-behavioural outcome linkages for the P3, ERN and (to a lesser extent) Pe appearing to reflect enhancement of existing neurocognitive patterns and/or in some cases closer resemblance to patterns seen in neurological healthy individuals. However, the “Stop!” strategy at the core of GMT is a cue that aims to compensate for – rather than directly restore – patients’ reduced capacity to endogenously sustain attention. That is, GMT is primarily oriented at reducing functional disability in the context of everyday activities. Both theoretically (Robertson & Murre, 1999) and empirically – based on the current and prior studies – GMT appears feasible and useful for patients across a broader spectrum of injury severity compared to computer-based retraining programs.

Even so, GMT itself requires sufficiently preserved motivational and cognitive capacity to engage in program activities and translate them into reliable everyday use. Two patients did not appear to benefit from GMT and two others did not show benefit until six months post-training. Though it is always reasonable to expect some patients in any treatment group will show limited response, with the emphasis on group-level effects in an RCT design such individual differences tend to remain unexplored or even unreported. While the correlational investigation in the current study suggested no significant limiting effects of disease severity or co-morbid mood disturbance, future research should attempt to identify patient factors likely to limit – or enhance – the effectiveness of GMT and perhaps ideally include adjuvant treatment components to specifically address them within a holistic rehabilitation framework (Cicerone, et al., 2008; Wilson, 2002).
Data in the current study also provided promising if somewhat limited evidence as to the neurocognitive effects of GMT. Relations of ERP to behavioural changes were suggestive of improved performance monitoring and self-regulated, goal-driven attentional and executive control. However, with several correlations approaching but not reaching statistical significance the available data may not support strong conclusions regarding the neurobehavioural outcomes hypothesized for GMT in this study.

Although power analysis had suggested the sample size recruited for this study would be sufficient to detect treatment by time interaction effects, in the end these were statistically marginal or did not approach significance despite trends in the data. Replication in a larger study is recommended to clarify results. Particularly given the initial small sample sizes, subject attrition by the 6-month follow-up may have limited power to detect treatment effects and particularly their neurophysiological correlates. Further, while inclusion of patients across the RRMS-SPMS severity spectrum was done intentionally (in contrast to studies that have excluded those with SPMS), it may have introduced a larger-than-expected degree of within-group variability which had the unintentional effect of limiting detection of statistically significant between-group differences, or specifically their interaction with time.

Despite these limitations and particularly in the context of prior research support for GMT, the consistency of results across the multi-level outcome battery in the current study – including tests of executive-attentional processes, ERP-behavioural patterns and improvement in real-life functioning – achieved the primary aim of this project, which was to validate GMT as a potential rehabilitation approach for self-regulatory impairment in MS. Replication in a larger sample may be advisable to address some of this study’s limitations and seek statistically stronger evidence of effectiveness with clarification of the neuro-behavioural and longer-term effects of GMT in patients with MS.


Multiple Sclerosis International Federation (2010). *Global Economic Impact of Multiple Sclerosis*.


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Appendices

Appendix 1. EEG electrode array with scalp coordinates

(Source: In-house Biosemi manual, EEG lab, Rotman Research Institute, Baycrest, Toronto, ON, Canada. Used with permission.)
Appendix 2. Scatter plot of MS patients’ brain-behaviour scores relating self-reported executive dysfunction to disease severity indices (behavioural PLS)

Outlier (brain score) circled.
Appendix 3. Scatter plot of MS patients’ brain-behaviour scores relating mean ERP amplitudes (P3, ERN, Pe) to disease severity indices (behavioural PLS)
Appendix 4. Scatter plot of controls’ and MS patients’ brain-behaviour scores relating mean SART No-go error-related amplitudes (ERN, Pe) to test performance in the broader neuropsychological battery (behavioural PLS)
Appendix 5. Scatter plot of GMT and BHW patients’ brain-behaviour scores relating baseline-to-post-training changes in ERP amplitudes and cognitive test performance (behavioural PLS, LV 2)

Outliers (brain score) circled.