The effects of cannabis on cognitive function in patients with multiple sclerosis

by

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Abstract

While neuropsychological deficits have been reported in healthy individuals who use cannabis, data in patients with multiple sclerosis (MS) are lacking. Given that MS is associated with cognitive deterioration, the aim of this study was to determine the cognitive effects of inhaled or ingested cannabis in this population. Fifty MS patients (25 cannabis users and 25 non-users) completed the Minimal Assessment of Cognitive Function in MS battery of neuropsychological tests. Cannabis users had significantly poorer performance on measures of information processing speed, executive functions, and visuospatial perception, and were twice as likely to be classified as globally cognitively impaired. Similar results were found after controlling for potential confounding variables. This study provides evidence that prolonged cannabis use in MS patients is associated with poorer performance on cognitive domains commonly affected in this population. The therapeutic benefits patients may derive from using cannabis should be weighed against the associated cognitive side-effects.

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List of Abbreviations

11-OH-THC: 11-hydroxy-Δ-9-tetrahydrocannabinol

2-AG: 2-arachidonoylglycerol

ACC: Anterior Cingulate Cortex

AChEIs: Acetylcholinesterase Inhibitors

AIDS: Acquired Immune Deficiency Syndrome

ANART: American National Adult Reading Test

APA: American Psychiatric Association

APOE: Apolipoprotein E

APOE-E4: E4 Allele of Apolipoprotein E

BNPB: Brief Neuropsychological Battery

BRB-N: Brief Repeatable Battery of Neuropsychological Tests

BVMT-R: Brief Visuospatial Memory Test – Revised

CAMS: Cannabinoids in Multiple Sclerosis Study

CB: Cannabinoids

CB1: Cannabinoid Receptor 1

CB2: Cannabinoid Receptor 2

CIS: Clinically Isolated Syndrome

CNS: Central Nervous System

COWAT: Controlled Oral Word Association Test

CVLT-II: California Verbal Learning Test – Revised

D-KEFS: Delis-Kaplan Executive Function System

DMDs: Disease-Modifying Drugs

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition

EDSS: Expanded Disability Status Scale

EMIT: Enzyme Immunoassay

fMRI: Functional Magnetic Resonance Imaging

HADS: Hospital Anxiety and Depression Scale

IQ: Intelligence Quotient

JLO: Judgment of Line Orientation

LC/MS/MS: HPLC/tandem Mass Spectrometry

MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis

MFIS: Modified Fatigue Impact Scale

MMSE: Mini-Mental State Examination

MRI: Magnetic Resonance Imaging

MS: Multiple Sclerosis

NAGM: Normal Appearing Gray Matter

NAWM: Normal Appearing White Matter

NMDA: N-Methyl-D-aspartic Acid

PASAT: Paced Auditory Serial Addition Test

PET: Positron Emission Tomography

PPMS: Primary Progressive Multiple Sclerosis

PVSAT: Paced Visual Serial Addition Test

RRMS: Relapsing-Remitting Multiple Sclerosis

SCID-I: Structured Clinical Interview for the Diagnostic and Statistical Manual-Fourth Edition Axis I Disorders

SDMT: Symbol Digit Modality Test

SPMS: Secondary Progressive Multiple Sclerosis

THC: Δ-9-tetrahydrocannabinol

THC-COOH: 11-nor-9-carboxy-Δ-9-tetrahydrocannabinol

WAIS-IV: Wechsler Adult Intelligence Scale-Fourth Edition

WCST: Wisconsin Card Sorting Test

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CHAPTER 1: LITERATURE REVIEW

1.1 MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a demyelinating, autoimmune disease of the central nervous system (CNS) characterized by multifocal areas of white matter lesions disseminated in time and space. Although the earliest historical account of the disease dates back to the 14th century (Murray, 2005), MS was first described as a distinct disease by French neurologist Jean-Martin Charcot in 1868 who documented and wrote extensively about the disease after discovering "plaques" and scarring of tissue in the brain of a deceased young woman who had unexplained and treatment-resistant neurological problems (Charcot, 1868b). MS is now recognized as the commonest cause of neurological disability affecting young and middle-aged adults who often experience disabling symptoms that considerably restrict their social and occupational functioning and adversely affect their quality of life.

1.1.1 Pathology

MS is characterized by a process of demyelination, remyelination, oligodendrocyte depletion and astrocytic, as well as neuronal and axonal degeneration over time. The pathological hallmark of MS is multifocal regions of axonal demyelination, called plaques, in the spinal cord, optic nerves and the various regions of the brain, particularly the periventricular white matter, deep white matter, juxtacortical white matter, the corpus callosum, cerebellar peduncles and dorsolateral spinal cord (Bradley, 2008).

Disruption of the blood-brain barrier is a critical pathological process, resulting in perivascular extravacation of inflammatory cells. Histologically, active plaques are characterized by infiltration of inflammatory cells, primarily T cells and macrophages, which are believed to play an integral role in demyelination. In addition to structural injury to myelin, cellular infiltration and accumulation of immune modulators (cytokines, chemokines, and adhesion molecules) within the plaque and the periplaque area also interfere with nerve transmission and may be toxic to neuronal and axonal integrity. The degree of inflammatory cell infiltration is correlated with the extent of axonal damage (Goldman, 2007).

As a response to this injury, astroglial cells are activated and oligodendrocyte precursor cells proliferate, leading to partial remyelination of affected axons, which appear as shadow plaques representing thinly myelinated axons. While the inflammatory response tends to become gradually less prominent, a chronic active rim of inflammation with microglial activation remains at the border of the injured myelin. Over time, there is a gradual decline in the ability of the oligodendrocyte progenitor cells to differentiate into mature myelinating oligodendrocytes, leading to progressively less remyelination as the disease progresses (Bradley, 2008).

MS lesions can be detected by Magnetic Resonance Imaging (MRI). Areas of active inflammation and blood-brain barrier disruption can be visualized by intravenous administration of gadolinium-based agents. The MRI picture reveals hypointense lesions for up to 3-6 weeks (Cotton, Weiner, Jolesz, & Guttmann, 2003). Many of these gadolinium-enhanced lesions may persist in the form of hypointense T1 black holes representing axonal and neuronal destruction, whereas others become chronic zones of hyperintensity representing edema, gliosis, inflammation, demyelination, remyelination and axonal loss (For a review, see Grassiot, Desgranges, Eustache, & Defer, 2009).

In recent years, structural brain imaging studies have revealed that MS is characterized not only by white matter lesions, but also by variable degrees of cortical and subcortical atrophy reflecting brain volume loss (Grassiot et al., 2009). Longitudinal studies have found significant loss of grey and white matter volumes in MS patients over time (Horakova et al., 2008). Measures of brain volume and atrophy have shown stronger links to physical disability than lesion volumes (Sanfilipo, Benedict, Sharma, Weinstock-Guttman, & Bakshi, 2005).

1.1.2 Epidemiology

MS most commonly affects young and middle-aged adults between the ages of 15 to 40, although children and older individuals are sometimes affected as well. As with most autoimmune diseases, women are more commonly affected. In adults, women are three times more likely than men to be afflicted with MS, with this ratio greater in children and lower in those diagnosed after the age of 50. A significant increase has been found in the incidence of MS in women, but not men, in the last several decades, further increasing the sex ratio (Orton et al., 2006; Alonso & Hernan, 2008).

An estimated 2.5 million individuals are diagnosed with MS worldwide (Fox, 2009). The global distribution of MS varies with geography, with the prevalence of MS increasing with distance from the equator. The precise reasons for this pattern of global distribution are unclear although climate, diet, infections and sunlight exposure have been proposed as possible explanations (Kurtzke, 2000).

The incidence of MS, defined as the number of individuals diagnosed at a given time within a specified population, ranges from 2 to 350 per 100,000 individuals. Countries and regions are often described as being classified into one of three zones based on the incidence of MS: low, medium and high. Regions with low frequency of MS are those with fewer than 5 cases per 100,000 individuals (e.g., many parts of Asia and Africa), and those with medium frequencies have prevalences of 5-29 per 100,000 (e.g., most of Australia, the southern Mediterranean basin, Ukraine, South Africa, and most of the Caribbean regions and South America). High frequency regions are those with incidence rates exceeding 30 per 100,000. Among these regions are the United States, Canada, some parts of Australia and Russia, as well as most European countries (Kurtzke, 2000).

With an average incidence of 240 per 100,000, Canada ranks among the highest frequency zones in the world. An estimated 55,000 to 75,000 Canadians are diagnosed with MS and there are approximately 1,000 new cases per year in Canada (Poppe, Wolfson, & Zhu, 2008). Prevalences in Canada display geographical variations across the provinces and territories, with the Prairies and Atlantic regions showing incidence rates as high as 340 and 350 per 100,000, respectively (Beck, Metz, Svenson, & Patten, 2005). These geographical variations across Canada point to factors other than latitude as contributing to risk of MS.

1.1.3 Clinical Presentation

MS is a heterogeneous disease in that its clinical presentation differs in patients and even within the same patient at different times during the disease course. The most common symptoms include disturbances in the visual system (nystagmus, optic neuritis, diplopia), musculoskeletal system (e.g., muscle weakness, spasms, ataxia), sensory-tactile system (e.g., pain, hypoesthesias, paraesthesias), bladder and bowel (e.g., incontinence, frequency or retention),

and neuropsychological functioning. Other symptoms include fatigue, speech problems (e.g., dysarthria), sexual dysfunction, and sleep disorders (Raine, McFarland, & Hohlfeld, 2008).

In many cases, MS symptoms arise as acute periods of exacerbation, also known as a relapse or attack. A relapse or MS attack refers to a loss or impairment of one or more neurological functions persisting for more than 24 hours and typically lasting for 3 to 6 weeks. During an attack new symptoms may appear and existing symptoms may worsen. Administration of high doses of intravenous corticosteroids is generally effective at relieving the acute symptoms and reducing the duration of each episode. Because recovery of function is often incomplete, symptoms accumulate over the years, leading to progressively greater levels of disability (Raine, McFarland, & Hohlfeld, 2008).

While the most common clinical presentation is generally one of exacerbations followed by complete or partial remission, this is not always the case. MS is classified into several subtypes or patterns of progression with differences in disease characteristics, therapeutic options and prognosis. While each disease course is associated with some degree of progression over time, it is the rate and pattern of progression that defines the subtypes.

A clinically isolated syndrome (CIS) refers to a single neurological attack suggestive of demyelination but failing to meet the diagnostic criteria for MS. The episode usually resolves within several weeks to months with most patients experiencing little or no symptoms following the attack. However, approximately 70 percent of individuals experiencing CIS go on to develop MS (Raine, McFarland, & Hohlfeld, 2008).

The most common MS subtype is relapsing-remitting MS (RRMS), affecting approximately two-thirds of all patients. RRMS is characterized by neurological attacks that generally evolve over a period of days to weeks, followed by partial or complete recovery (remission) within weeks to months. In RRMS, there is no progression of neurologic impairment between attacks during periods of remission. Approximately 50 to 65 percent of patients with RRMS go on to develop Secondary Progressive MS (SPMS), characterized by gradual disease progression (worsening) between neurological attacks. The transition from RRMS to SPMS may occur shortly after disease onset or may be delayed for several years to decades (Raine, McFarland, & Hohlfeld, 2008).

A distinct subtype affecting 10 to 15 percent of all MS patients is Primary Progressive MS (PPMS), characterized by a progressive course from disease onset and the absence of distinct relapses. Patients with PPMS tend to be older at the time of disease presentation and a higher proportion are men. Studies suggest that the pathogenesis of PPMS may differ from the other subtypes in that PPMS patients generally show less inflammatory processes and more axonal loss and microglial activation in normal appearing brain tissue (Raine, McFarland, & Hohlfeld, 2008).

1.1.4 Etiology

The precise etiology of MS is largely unknown but is considered to be multifactorial, involving the interplay between environmental and genetic factors. A number of factors have been postulated as etiologically significant. A family history of MS increases the risk of developing the disease, suggesting genetic etiology. Indeed, approximately 20 percent of MS patients have at least one affected relative (Ebers, Sadovnick, Risch, & the Canadian Collaborative Study Group, 1995). Studies examining the role of genetic factors in MS have reported that 20 locations within the genome may contribute to varying degrees to susceptibility to MS (National Multiple Sclerosis Society, 2002). The most direct evidence for a genetic etiology has been derived from twin studies. Studies have consistently found that monozygotic twins have greater concordance rate for MS compared to dizygotic twins. Siblings and dizogotic twins have on average a 2 percent concordance rate for MS whereas monozygotic twins have a 40 percent concordance rate (Pryse-Phillips, 1996). However, despite the fact that dizygotic twins and non-twin siblings are genetic equivalents, non-twin siblings have reportedly lower concordance rate compared to dizygotic twins (Cendrowski, 1968), suggesting a possible mediating role of early environmental experiences more commonly shared by twins. The role of environmental factors is also supported by the 60 percent discordance rate among monozygotic twins despite identical genetic predispositions. Therefore, genetics certainly plays a critical, albeit not absolute, role in determining susceptibility to MS.

Residing in a region with a high prevalence of MS early in life is a risk factor for developing the disease (Dean and Kurtzke, 1971; Hammond, English, & McLoed, 2000; Elian, Nightingale, & Dean, 1990). Studies have found that areas with low levels of ultraviolet radiation have higher prevalences of MS (Beretich & Beretich, 2009) and that ultraviolet B radiation is more closely

associated with the risk of MS than latitude alone (Kampman & Brustad, 2008; Sloka, Pryse-Phillips, & Stefanelli, 2008; van der Mei et al., 2003). Indeed, there is a lower risk of MS with increasing serum vitamin D levels in individuals of Caucasian descent (Munger, Levin, Hollis, Howard, & Ascherio, 2006). A similar association between vitamin D status and risk of MS has been found in children with a first episode of CNS demyelination (Hanwell et al., 2008). Evidence is also emerging that vitamin D insufficiency may influence disease progression by increasing the risk of relapse (Smolders, Menheere, Kessels, Damoiseaux, & Hypperts, 2008) and potentially contributing to higher levels of disability after controlling for the influence of disability on sunlight exposure (Smolders et al., 2008; van der Mei et al., 2007). The association between vitamin D status and risk of relapse has also been reported in pediatric-onset MS (Mowry et al., 2010).

1.1.5 Diagnosis

A diagnosis of MS can be made based on clinical presentation in patients displaying two or more episodes of neurological attacks suggestive of different neural networks. However, the clinical manifestations of MS are widely varied and the heterogeneity of symptom presentations may elude diagnosis. More recent diagnostic criteria for MS make use of advances in MRI techniques as well as clinical presentation to affirm a diagnosis of MS (McDonald et al., 2001). Sites of demyelination can be visualized on MRI scans as focal or confluent lesions in white matter tracts disseminated in space (localization in two or more brain regions) and time (new plaques appearing over time).

1.1.6 Treatment

There is no known cure for MS but there are various therapies aimed at reducing the rate of disease progression and managing the symptoms associated with MS. Several immunomodulating agents known as disease-modifying drugs (DMDs) have been approved for use with MS patients and have shown modest effectiveness in decreasing the number of neurological attacks and the rate of disease progression. These include interferon beta-1a, interferon beta-1b, glatiramer acetate, and natalizumab. All DMDs have shown modest efficacy in slowing the progression of the disease and reducing the frequency of relapses, particularly in patients with RRMS. Mitoxantrone, an antineoplastic agent, has shown promising results in

patients with SPMS. In addition, MRI findings suggest that immunomodulatory drugs reduce total lesion load and the number of active lesions in the brain. There are currently no acceptable treatments that modify the course of PPMS (Li & Paty, 1999; Simon et al., 1998).

The few open-label clinical trials of vitamin D therapy in individuals with MS have reported that dosages as high as 40,000 IU/day of vitamin D3 are safe and may be effective at reducing lesion volume (Kimball, Ursell, O'Connor, & Vieth, 2007) and relapse frequency (Myhr, 2009).

1.2 NEUROPSYCHOLOGICAL PROFILE OF MULTIPLE SCLEROSIS

In his description of MS, Charcot noted that many patients suffer from a "marked enfeeblement of the memory; conceptions that formed slowly; the intellectual and emotional faculties are blunted in their totality" (Charcot, 1868b). Although neuropsychological testing in MS research was employed as early as the 1950s (Ross & Reitan, 1955), it was not until the late 1970s when several controlled studies using standardized, objective neuropsychological measures found that cognitive dysfunction may in fact be far more prevalent in this group than originally thought. Nonetheless early investigators viewed these cognitive deficits as most likely secondary to motor deficits (Beatty & Gange, 1977).

In a study which remains a pivotal turning point in MS and cognition research, Rao, Leo, Bernardin, and Unverzagt (1991a) administered a comprehensive neuropsychological battery consisting of 31 cognitive indices, to 100 community-based MS patients and 100 demographically-matched healthy controls. Defining the lowest fifth percentile of scores of healthy control subjects as the cutoff for "failure" on each measure, they found that 48 of 100 MS patients failed on 4 or more of the cognitive indices.

Today cognitive impairment is recognized as one of the most common clinical characteristics of MS, with prevalence estimates ranging from 43-46 percent in community-based samples (Rao et al., 1991a; McIntosh-Michaelis et al., 1991) to 54-65 percent in clinic-based patients (Peyser, Edwards, Poser, & Filskov, 1980; Heaton, Chelune, Talley, Kay, & Curtiss, 1985; Staples & Lincoln, 1979; Lyon-Caen et al., 1986), the latter group having higher levels of disease-related disability.

Although the cognitive profile differs from patient to patient and even within the same patient over time, several generalizations can be made regarding the nature of cognitive impairment in MS. Cognitive deficits in MS patients are focal rather than global, subtle in their presentation, and often evade detection during routine clinical examination (Benedict et al., 2002). Striking cognitive deficits such as dementia, aphasias and agnosias are rare (Fischer, 2001).

1.2.1 Estimating Premorbid Intelligence

In the absence of neuropsychological assessment prior to the onset of MS, it is difficult to determine the degree to which patients' cognitive performance has been affected by the disease. Thus, several measures of premorbid intelligence can be used in order to provide a crude estimate of pre-MS cognitive abilities.

The gold standard measure of intelligence is the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler, Coalson, & Raiford, 2008), which provides scores for Full Scale intelligence quotient (IQ), as well as constituent subscores for Verbal and Performance (non-verbal) IQ. However, the Performance subscales of the WAIS-IV are often timed and require intact manual dexterity, making administration of these subscales difficult for MS patients with physical limitations. Furthermore, the administration time for the WAIS-IV is generally between 60-75 minutes, making it unfeasible for use as part of a larger neuropsychological battery to assess present cognitive functioning.

Reading tests such as the American National Adult Reading Test (ANART; Nelson, 1982), which assess vocabulary knowledge as a proxy for verbal IQ, are widely believed to provide robust estimates of premorbid intelligence, specifically verbal IQ (Crawford, Deary, Starr, & Walley, 2001; Moss & Dowd, 1991). The premise for using vocabulary to estimate premorbid intelligence relies on findings that suggest that in the general population, vocabulary knowledge and IQ are highly correlated (Crawford, Stewart, Cochrane, Parker, & Besson, 1989). Furthermore, reading abilities are believed be resistant to the effects of brain pathology and are retained in individuals with dementia (Sharpe & O'Carroll, 1991).

There is some disagreement on the extent to which MS patients experience decline in general intelligence. On measures of verbal IQ, some cross-sectional studies have found no significant difference between MS patients and healthy controls (McIntosh-Michaelis et al., 1991; Drew,

Tippett, Starkey, & Isler, 2008; Smestad, Sandvik, Landro, & Celius., 2010) whereas others have reported slightly lower scores in MS patients (Rao et al., 1991a). Longitudinal studies have reported slight declines in IQ as the disease progresses (Bernardin, Rao, & Luchetta, 1993; Ron, Callanan, & Warrington, 1991). Still other studies suggest that performance IQ is more affected by MS than verbal IQ (Rao, 1986). While the precise reasons for this latter finding are unclear, the timed nature of some of the WAIS-IV Performance subtests as well as their reliance on manual dexterity may explain this discrepancy.

Studies have shown that higher premorbid intellectual abilities can moderate the effects of MS-related brain pathology on cognition (Sumowski, Wylie, Chiaravalloti, & DeLuca, 2010), allowing MS patients with higher premorbid intelligence to maintain a higher level of cognitive functioning compared to those with lower premorbid intelligence (Sumowski, Chiaravalloti, Wylie, & DeLuca, 2009).

1.2.2 Information Processing Speed

Information processing speed refers to the capacity to process information rapidly, and its impairment is the hallmark of cognitive decline in MS, affecting over half of all patients (Rao et al., 1991a; Litvan, Grafman, Vendrell, & Martinez, 1988; Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007b; Denney, Lynch, Parmenter, & Horne, 2004; Denney, Lynch, & Parmenter, 2008). Slowed responding cannot be attributed to impaired motor functioning because deficits in this domain have been demonstrated across multiple modalities (i.e., auditory, visual-motor).

One of the most commonly used measures of cognitive functioning in MS is the Paced Auditory Serial Addition Test (PASAT), which taps into sustained and divided attention and working memory in addition to speed of information processing speed (Gronwall, 1977). MS patients consistently perform poorly on the PASAT, regardless of the rate of inter-stimulus presentation (Rao et al., 1991a; Litvan et al. 1988). Similar deficits have been found in a visual version of this task, the Paced Visual Serial Addition Test (PVSAT), in patients with MS (Diamond, DeLuca, Heakyung, & Sharon, 1997) and those with CIS (Feinstein, Youl, & Ron, 1992). However, results of the PASAT must be interpreted with caution given the relationship between

scores on this measure on the one hand, and age, premorbid intelligence, and mathematical abilities on the other (Tombaugh, 2006).

Another commonly used cognitive test is the Symbol Digit Modality Test (SDMT), a complex measure of information processing speed, attention and working memory (Smith, 1982). The SDMT is perhaps the most sensitive cognitive screening tool in both clinical and research settings (Parmenter et al., 2007b) and has shown strong correlations with measures of brain atrophy (Benedict et al., 2005a). Recent findings also suggest that compared to other well-established measures of cognitive functioning, the SDMT more accurately reflects qualitative, self-reported cognitive impairment (Drake, Schwartz, Weinstock-Guttman, Munschauer, & Benedict, 2008).

The importance of information processing speed deficits in MS is highlighted by findings that suggest that slowed information processing speed could be at least in part responsible for deficits in other cognitive domains, such as memory (DeLuca, Barbeiri-Berger, & Johnson, 1994; Litvan et al., 1988) and executive functioning (Denney et al., 2004). Deficits in information processing speed, as measured by the SDMT, have also been associated with greater deterioration in neurological function at 5 and 7 year follow-ups (Deloire, Ruet, Hamel, Bonnet, & Brochet, 2010).

1.2.3 Learning and Memory

As many as 40 to 60 percent of MS patients show deficits on measures of learning and memory (Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988; Grant, McDonald, Trimble, Smith & Reed, 1984; Minden, Moes, Orav, Kaplan, & Reich, 1990; Rao, Hammeke, McQuillen, Khatri, & Lloyd, 1984; Staples & Lincoln, 1979). Memory is a complex cognitive process and various subtypes of memory are differentially affected in patients with MS. A distinction has been made between explicit (declarative) and implicit (procedural) learning in the cognitive neuroscience literature (Squire, 2004). MS patients perform within normal limits on measures of procedural learning, such as semantic priming (Blum, Yonelinas, Luks, Newitt, Oh, Lu et al., 2002; Latchford, Morley, Peace, & Boyd, 1993; Scarrabelotti & Caroll, 1998) and skill learning (Beatty, Goodkin, Monson, & Beatty, 1990). Conversely, deficits in immediate and long-term

declarative memory are widespread (Beatty & Gange, 1977; Litvan et al., 1988; Heaton et al., 1985; Beatty et al., 1988).

Using word-list learning tasks to measure immediate and long-term declarative memory, early studies showed that MS patients perform poorly on tests of immediate free recall, usually from the first acquisition trial (Beatty & Gange, 1977; Litvan et al., 1988). Similar deficits have been found on measures of visuospatial memory where MS patients tend to recall fewer items from an array of geometric shapes or objects (Ryan, Clark, Klonoff, Li & Paty, 1996; Fischer, 1988; Heaton et al., 1985; Van den Burg, van Zomeren, Minderhoud, Prange, & Meijer, 1987; Beatty et al., 1988; Rao et al., 1984; 1991).

Declarative memory involves the encoding, consolidation and retrieval of previously presented information. Deficits in any one of these processes can lead to impaired memory. Early investigations attributed impaired long-term memory in MS patients to a failure in *retrieval* processes (Thornton & Raz, 1997; Rao, Leo, & St. Aubin-Faubert, 1989a). In support of this view, studies have consistently found that only free recall of previously learned words, but not recognition memory, is adversely affected in MS patients (Thornton & Raz, 1997), which suggests that even though the information has been encoded (patient is able to recognize which words were previously presented), deficits in retrieval processes may be responsible for impaired free recall.

Other investigators have proposed that deficits in *encoding* or acquisition processes underlie long-term memory impairment in MS (DeLuca et al., 1994; Demaree, Gaudino, DeLuca, & Ricker, 2000). This implies that when patients fail to recall previously presented information as is observed in free recall trials, it is because the information was never "encoded" during the acquisition phase. In a study in which subjects were permitted as many trials as necessary in order to memorize a list of 10 words, DeLuca et al. (1994) found that MS patients required twice as many trials as healthy controls to learn the list but that their performance on the delayed recall condition was similar to controls. That MS patients required more trials to encode the words points to difficulties in the initial acquisition of information, whereas their normal performance on the delayed free-recall suggests that retrieval processes are intact once information has been encoded. It is plausible that deficits in encoding may be a result of attentional and information processing deficits, which may interfere with the ability to process

the word list rapidly enough for encoding to occur (Beatty, 1993; Grant et al., 1984; Grisby, Ayarbe, Kravcisin, & Busenbark, 1994; Litvan et al., 1988; van den Burg et al., 1987).

A plausible synthesis of these findings is the view that deficits in the various components of memory processing (i.e., encoding and retrieval) may represent a continuum of severity in memory dysfunction, whereby deficits in one of these processes may underlie mild memory impairment while deficits in both encoding and retrieval leads to more severe impairment. This view is supported by the findings of one study (Beatty et al., 1996) that MS patients can be separated into three groups based on results of a memory test: those with no memory impairment, those with deficits in retrieval only, and those with deficits in encoding and retrieval. Interestingly, there was no difference in disease duration between the groups, suggesting that memory decline does not necessarily follow a gradual, progressive course over time (Beatty et al., 1996).

Notwithstanding the precise nature of memory impairment, there is abundant evidence that MS patients are highly susceptible to deficits in various learning and memory subdomains. Long-term memory is an ecologically valid indicator of daily functioning (Higginson, Arnett, & Voss, 2000) and deficits have been associated with greater deterioration in neurological functioning at 5 and 7 year follow-up (Deloire et al., 2010).

1.2.4 Executive Functioning

Executive functioning is a broad term referring to the set of higher-order cognitive processes that direct complex behaviours such as response inhibition, mental set shifting, abstraction, initiation, planning, problem solving, and cognitive flexibility. Deficits in executive functioning are paramount in MS, especially in patients with SPMS and PPMS (Heaton et al., 1985; Rao et al., 1991a) and are attributed to prefrontal lobe functioning (Foong et al., 1997). Approximately 15 to 20 percent of MS patients show deficits in one or more executive processes (Drew et al., 2008; Fischer, 2001; Rao et al., 1991a), although one study employing a more comprehensive battery found that two-thirds of their sample had deficits on one or more executive function indices (Drew et al., 2008).

The Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993) has become a gold standard in measuring executive functioning, tapping into set shifting, abstract

reasoning, and conceptual reasoning. Studies have found significantly fewer correct responses and more perseverative errors on the WCST in MS patients compared to healthy controls (Beatty & Monson, 1996; Rao, Hammeke, & Speech, 1987; Parmenter et al., 2007a).

Another commonly used measure of executive functioning is the Sorting Test, which is part of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001). In this test, subjects are given a set of cards with various features and attributes and are instructed to arrange the cards into two groups in as many different ways as possible, each time ensuring that each group of cards has at least one commonality. MS patients consistently achieve a lower number of correct sorts, a lower description score and more frequent perseverations (Parmenter et al., 2007a; Beatty & Monson, 1996). Although both the Sorting Test and the WCST tap into conceptual thinking, set shifting and perseveration, the Sorting Test has become the recommended measure of executive functioning in MS patients because it provides separate measures for the component processes (i.e., perseverations vs. concept formation) and is a more robust measure of executive functions (Parmenter et al., 2007a).

1.2.5 Visuospatial Perception

As previously mentioned, gross abnormalities in perceptual function such as visual agnosia are rare in patients with MS (Fischer, 2001). However, more subtle deficits in visuospatial processing, which refers to the ability to accurately perceive and discriminate objects or make spatial judgments, affect over one-fifth of MS patients (Benedict et al. , 2006). MS patients have shown deficits on a wide array of visuoperceptual tests (i.e., detection and recognition of shapes, objects or faces, or colour perception; Vleugels et al., 2001) and spatial orientation (i.e. discrimination of line orientation; Rao et al., 1991a).

Deficits in visuospatial processing are present even on tests that do not rely on manual dexterity (Rao et al., 1991a), only weakly related to visual acuity (Rao et al., 1991a; Vleugels et al., 2001), and independent of performance on other neuropsychological tests (Vleugels et al., 2001). While the latter finding suggests that visuoperceptual function represents a distinct cognitive domain, slowed information processing speed has been proposed as one of the factors underlying visuoperceptual impairment (Vleugels et al., 2001).

1.2.6 Verbal Fluency

While MS patients retain general language comprehension abilities, other language functions such as word retrieval (or verbal fluency) are often adversely affected (Rao et al., 1991a; Beatty & Monson, 1996; Beatty et al., 1995b; Beatty, Goodkin, Monson, Beatty, 1989; Krupp, Sliwinski, Masur, Friedberg, & Coyle, 1994; Ryan et al., 1996; Sperling et al., 2001). Verbal fluency refers to the ability to rapidly generate words within a given time frame while simultaneously adhering to a set of phonemic or semantic rules.

MS patients perform poorly on both semantic and phonemic fluency tests (Beatty, 2002; Parry, Scott, Palace, Smith, & Matthews, 2003), although studies are divided on which is more adversely affected (Nocentini et al., 2001; Zakzanis, 2000). A recent meta-analysis concluded that the sensitivities of the two measures are similar (Henry & Beatty, 2006). Regardless of the specific task employed, approximately 13 to 23 percent of MS patients score in the borderline to impaired range (Benedict et al., 2006; Rao et al., 1991a; McIntosh-Michaelis et al., 1991).

Verbal fluency tasks engage several cognitive domains, including working memory, information processing speed and executive functions (Lezak, 1995; Spreen & Strauss, 1998) although the extent to which each of these domains contribute to performance is unclear. Verbal fluency is believed to reflect executive functioning (Rosser & Hodges, 1994), and meta-analyses have shown measures of verbal fluency to be robust indicators of executive dysfunction (Wishart & Sharpe, 1997; Zakzanis, 2000). However, given the "speeded" nature of verbal fluency tasks, information processing speed is likely to play a critical role (Salthouse, Atkinson, & Berish, 2003; Henry & Beatty, 2006) and deficits are also likely to reflect the inability to process thoughts, cross-reference their accuracy against a set of rules, and produce responses rapidly (Beatty, 1993).

1.2.7 Neuropsychological Assessment in Multiple Sclerosis

Detection of cognitive dysfunction in patients with MS remains a challenge today as objective neuropsychological assessments are not commonly performed during routine clinical examinations. Given the subtle and heterogeneous cognitive profile of MS patients, measures of general cognitive abilities such as the Mini-Mental State Examination (MMSE) used to screen for dementia, fail to show clinically meaningful deficits in MS patients (Janculjak, Zdenko,

Brinar, & Spilich, 2002) and have a 70 percent false negative rate (Beatty & Goodkin, 1990; Mahler, Davis, & Benson, 1989). Self-report questionnaires probing cognitive difficulties in have been developed as quick screening tools (Benedict et al., 2003), but their utility is questionable especially since MS patients tend to demonstrate deficient metamemory, which is required in order to accurately appraise one's own cognitive abilities (Beatty & Monson, 1991). Informant-based reports appear to provide a more reliable assessment of cognitive functioning in patients, but these too may be susceptible to certain biases (Benedict et al., 2003). Therefore, objective neuropsychological examination is necessary in order to accurately detect the subtle and specific deficits commonly observed in MS.

In order to standardize the assessment of cognitive functioning in MS, several neuropsychological test batteries have been developed. Of these, the most widely used is the Brief Neuropsychological Battery (BNPB) which was a derivative of the first large scale study of cognition in community-based MS patients (Rao et al., 1991a). The 25-minute screening battery includes four neuropsychological tests that were determined to be the most sensitive to cognitive dysfunction in MS: Buschke Verbal Selective Reminding Test as a measure of verbal/auditory memory; 7/24 Spatial Recall Test to assess visuospatial memory; PASAT as a measure of working memory and information processing speed; and the Word List Generation, a measure of verbal fluency and word retrieval. A modified version of this battery, called the Brief Repeatable Battery of Neuropsychological Tests (BRB-N; Rao, 1990), was developed based on the recognition of the necessity of alternate forms of neuropsychological tests allowing for repeated testing to examine the progression of cognitive function in MS. The BRB-N is distinct from the BNPB in its inclusion of the SDMT as an additional measure of information processing speed and attention, the inclusion of a shorter version of Buschke Verbal Selective Reminding Test, and the replacement of the 7/24 Spatial Recall Test with a more challenging version called the 10/36 Spatial Recall Test.

In 2001, an international panel of neuropsychologists and neurologists, after reviewing the extant literature on MS and cognition, recommended the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2002) as the optimal battery for assessing neuropsychological performance in patients with MS. The 90-minute battery includes 7 tests measuring 5 cognitive domains most commonly affected in MS patients including: (a) Verbal learning and memory: The California Verbal Learning Test – Revised (CVLT-II); (b)

Visuospatial memory and learning: Brief Visuospatial Memory Test-Revised (BVMT-R); (c) Visuospatial perception: The Judgment of Line Orientation (JLO); (d) Verbal fluency/ word retrieval: The Controlled Oral Word Association Test (COWAT); (e) Executive functions: The D-KEFS Sorting Test; (f) Information processing speed and working memory: PASAT with 3- and 2-second inter-stimulus intervals; (g) Information processing speed: SDMT.

These tests were selected for inclusion in the battery for their acceptable test-retest reliability, available normative data, adequate range (minimal ceiling and floor effects), adequate discrimination between MS patients and controls, availability of equivalent alternate forms for repeated testing, and ease of administration. The MACFIMS has since been validated in several prospective samples (Benedict et al., 2005b; Benedict et al., 2006; Parmenter et al., 2007b). With cognitive impairment on each test defined as a z score of less than -1.5 on two or more of the 11 cognitive indices, 59.5 percent of MS patients were classified as cognitively impaired according to the MACFIMS (Benedict et al., 2006).

1.2.8 Correlates of Neuropsychological Impairment in Multiple Sclerosis

Socio-Demographic Factors

It is evident from the literature on the general population that cognitive functioning depends on various socio-demographic factors including age (Hofer & Alwin, 2008), sex (Caplan, Crawford, Shibley Hyde, & Richardson, 1997), and education (Friedman, Klivington, & Peterson, 1986). However, in the MS literature, very few studies have examined the interaction between MS-related cognitive deficits and demographic variables.

With respect to the effect of aging, there is no evidence to suggest a more rapid pattern of age-related cognitive decline in MS patients compared to controls. A cross-sectional study of the interaction between age and MS-related decline in information processing speed found that while MS patients were slower than controls at all ages, and older individuals slower than younger subjects, age-related declines were similar in MS patients and controls (Bodling, Denney, & Lynch, 2009).

The few studies that have examined the effect of sex on cognitive performance in MS found that male patients had poorer performance on measures of verbal and non-verbal recall, delayed verbal recognition, information processing speed, facial recognition, semantic fluency, and executive functioning (Beatty, Goodkin, Hertsgaard, & Monson, 1990; Beatty & Aupperle, 2002). These effects were independent of age at testing, age of disease onset, physical disability, and disease duration and course. In healthy controls, these sex differences were either nonexistent or present to a much lesser degree (Beatty & Aupperle, 2002).

As previously discussed, high premorbid intelligence has been shown to serve as a protective factor against the progression of cognitive deficits in patients with MS (Sumowski et al., 2009; 2010). Similarly, evidence has emerged to suggest that MS patients with higher educational attainment tend to have higher cognitive functioning (Fuvesi et al., 2010; Bonnet et al., 2006), suggesting that premorbid intellectual enrichment may moderate the effects of brain pathology on cognitive functioning.

Disease-Related Variables

In MS patients, demographic factors interact with various disease-related parameters such as disease course, disease duration and neurological disability to determine an individual's susceptibility to cognitive impairment. A chronic progressive disease course, which includes SPMS and PPMS, has been associated with poorer performance on measures of information processing speed (Janculjak et al., 2002; De Sonneville et al., 2002), verbal fluency (Friend et al., 1999), executive functioning (Heaton et al., 1985; Rao et al., 1987), and memory (Beatty et al., 1988; Rao et al., 1984; Minden & Moes et al., 1990; Brassington & Marsh, 1998). Attempts to delineate the likelihood of cognitive impairment in each chronic progressive subtype however, have led to conflicting results, with some studies finding higher rates of cognitive impairment in PPMS patients (Fuvesi et al., 2010) and others reporting rates as low as 7 percent in those with PPMS (Comi et al., 1995).

Interestingly, the relationship between chronic progressive disease course and more severe cognitive deficits is attenuated when age, neurological disability, and duration of illness are factored into analysis (Henry & Beatty, 2006). This suggests that advanced age, greater

disability and longer duration of illness, which often accompany a chronic progressive disease course, may account for the relationship between disease course and cognition.

The relationship between disease duration, physical disability and cognitive functioning has been the subject of many investigations. Early studies found strong correlations between motor functioning and memory in MS patients (Beatty & Gange, 1977). However, more recent studies using cognitive measures that are less dependent on motor functioning have shown that cognitive deficits do not necessarily arise in parallel with other neurological symptoms. Even in patients with little or no physical disability, deficits have been found in long-term and working memory (Klonoff, Clark, Oger, Paty, & Li, 1991; Pelosi, Geesken, Holly, Hayword, & Blumhardt, 1997; Ruggieri, Palermo, Vitello, Gennuso, Settipani, & Piccoli, 2003; van den Burg et al., 1987), abstract reasoning (Ruggieri et al., 2003), divided attention (Tinnefeld, Treitz, Haase, Wilhelm, Daum, & Fraustmann, 2005), visuo-constructive functions and short-term visual recognition memory (Haase, Tinnefeld, Lienemann, Ganz, & Faustman, 2003). One study (Smestad et al., 2010) found that three decades after disease onset, 26 percent of patients had only mild physical disability and nearly 40 percent did not require walking aids, whereas 48 percent were cognitively impaired in at least two of four cognitive domains assessed. While the absence of neurological disability does not necessarily represent the status of cognitive functioning, greater neurological disability has been associated with more deficits on measures of executive functioning (Drew et al., 2008), reaction time, divided attention, and visual recognition (Tinnefeld et al., 2005; Fuvesi et al., 2010). The relative dissociation between physical and cognitive functioning may be because disability scales such as the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), are primarily focused on ambulatory and neurological deficits, with little or no emphasis on higher cortical functioning (Kessler, Cohen, Lauer, & Kausch, 1991). It has been proposed that differences in the site of brain pathology may explain the presence of cognitive deficits in the absence of noticeable physical disability (Brassington & Marsh, 1998).

It is now widely believed that cognitive deficits appear early in the disease process. Cognitive deficits have been found in patients with clinically isolated syndromes (Callanan, Logsdail, Ron, & Warrington, 1989; Feinstein et al., 1992) and in those with probable MS undergoing the diagnostic process (Achiron & Barak, 2003). Longitudinal studies have confirmed that cognitive impairment can occur early in the disease and is an independent predictor of deficits in everyday

functioning (Amato, Ponziani, Siracusa, Sorbi, 2001), and predicts scores of functional disability such as the Activities of Daily Living (Kessler et al., 1991). In a long-term controlled study of cognitive functioning, Amato et al. (2001) found deficits on tests of verbal memory and abstract reasoning at baseline in patients with early-onset MS. These deficits were retained at 4.5 years follow-up, at which time patients also had poorer performance on measures of verbal fluency and comprehension. At 10 years follow-up, deficits in short-term verbal memory, attention, and short-term spatial memory were also present. These findings suggest that in addition to the early onset of cognitive deficits, the overall trend is one of worsening cognition over time. The proportion of impaired patients and the range of neuropsychological functions affected increases with disease progression and greater disability (Amato et al., 2001; Haase et al., 2004).

Genetic Susceptibility

The search for genetic biomarkers that predispose MS patients to cognitive dysfunction has focused on the gene that codes for apolipoprotein E (APOE), a ubiquitous protein with a role in metabolism of cholesterol and involved in regeneration of axons and myelin repair. The E4 allele of APOE has been associated with Alzheimer's disease as well as cognitive deficits in non-demented elderly individuals. Among patients with MS, the results have been inconclusive, with some studies finding an association between the APOE-E4 genotype and cognitive dysfunction (Koutis, 2007; Shi, Zhao, Vollmer, Tyry, & Kuniyoshi, 2008) whereas others reporting no association (Portaccio et al., 2009; Ghaffar, Reis, Pennell, O'Connor, & Feinstein, 2010). Thus the role of APOE-E4 in cognitive impairment in MS remains to be determined.

Psychiatric Factors and Fatigue

Depressive and anxiety disorders are common in MS patients with lifetime prevalences of 25 to 54 percent (Patten, Beck, Williams, Barbui, & Metz, 2003; Sadovnick et al., 1996; Minden & Schiffer, 1991) and 36 percent (Galeazzi et al., 2005; Korostil & Feinstein, 2007), respectively. While emotional and psychiatric disturbances often accompany cognitive deficits, the causal link is unclear. While depression is not linked to automatic cognitive processing, it has been related to deficits in a host of effortful cognitive domains in MS, most notably in executive functioning (Arnett, Higginson, & Randolph, 2001; Denney et al., 2004; Arnett et al., 1999a,

1999b; Gilchrist & Creed, 1994) as well as information processing speed, attention and working memory (Arnett et al., 1999a; 1999b; Thornton & Raz, 1997). Deficits in learning and information processing speed have been found to vary as a function of the severity of depression (Demaree, Gaudino, & DeLuca, 2003). While it is plausible that cognitive deficits can lead to depressive symptoms, the more plausible explanation is that deficits in executive functioning are exacerbated by major depression, leading to adverse effects on other cognitive domains (For a review, see Feinstein, 2005).

The number of publications devoted to anxiety disorders associated with MS pales in comparison to the literature on depression. Anxiety is a common concomitant of MS with elevated rates reported for generalized anxiety disorder, obsessive compulsive disorder (Korostil & Feinstein, 2007) and social anxiety (Poder et al., 2009). Few studies have explored the effect of anxiety on cognitive performance in patients with MS. Higher anxiety scores have been found in cognitively impaired patients (Simioni, Ruffieux, Bruggimann, Annoni, & Schluep, 2007) and are associated with poorer executive functioning (Stenager, Knudsen, & Jensen, 1994). Using the State-Trait Anxiety Inventory, Julian and Arnett (2009) found that State but not Trait anxiety was associated with poorer performance on an index of speeded executive functioning even after controlling for the effects of depressive symptoms. The authors suggest that State anxiety (apprehension and worry) places additional demands on the central executive system, depleting processing resources and leading to poorer efficiency in tasks of speeded executive functioning (Julian & Arnett, 2009).

Fatigue is one of the most consistently reported symptoms of MS, endorsed by nearly two-thirds of all patients and associated with adverse effects on quality of life (Egner, Phillips, Vora, Wiggers, 2003). The effect of fatigue on cognition, particularly on speeded tasks, has been widely investigated, although the link between the two remains unclear.

There is a strong association between fatigue as measured by self-report questionnaires and subjectively reported cognitive deficits (Fraser & Stark, 2003; Parmenter, Denney, & Lynch, 2003). Studies using objective neuropsychological measures have found a similar association between self-reported fatigue and information processing speed (Diamond, Johnston, Kaufman, & Graves, 2008).

Conversely, other studies have failed to find an association between fatigue and cognitive functioning (Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009). Similarly, Parmenter and colleagues (2003) found no differences in cognitive performance in MS patients undergoing cognitive testing during periods of high fatigue versus periods of low fatigue (Parmenter et al., 2003).

While several investigators have pointed to a distinction between various forms of fatigue, namely physical and cognitive fatigue and lassitude (defined as a general subjective sense of reduced energy) in MS patients (Schwid, Covington, Segal, & Goodman, 2002), studies examining fatigue and its impact on cognition have often failed to consider these distinctions. Cognitive fatigue, defined as a decline in cognitive performance during sustained cognitive activity (Schwid et al., 2002), may represent a salient confounding variable in cognitive studies of MS patients. Indeed, Krupp and Elkins (2000) found that unlike healthy control subjects who showed a gradual improvement in cognitive performance across a single 4-hour test session, MS patients showed a decline on measures of verbal memory and conceptual planning (Krupp & Elkins, 2000). While the link between fatigue and cognitive deficits is far from clear, it is important for future studies to independently quantify between the various forms of fatigue.

Neuroimaging Studies

Various neuroimaging techniques have been employed to better understand the relationship between CNS pathologies and cognitive impairment in MS. MRI studies have linked global markers of impaired cognition to hyper- and hypo-intense lesion volumes (Lazeron et al., 2005; Sperling et al., 2001; Karlinska, Siger, Lewanska, & Selmaj, 2008; Brass, Benedict, Weinstock-Guttman, Munschauer, & Bakshi, 2006). Total lesion burden has shown moderate to strong correlation with individual cognitive measures as have regional measures of lesion load (Lazeron et al., 2005; Franklin, Heaton, Nelson, Filley & Seibert, 1988). Specifically, measures of visuospatial memory and learning have been correlated with parietal lesion load, whereas measures of information processing speed, working memory and verbal fluency have been associated with frontal, parietal and temporal lesion loads (Lazeron et al., 2005).

In recent years, the prominent role of cerebral atrophy in cognitive dysfunction has been demonstrated (Sanchez, Nieto, Barroso, Martin, & Hernandez, 2008; Lazeron et al., 2005;

Benedict, Carone, & Bakshi, 2004). In a detailed MRI analysis, Benedict et al. (2004) found that third ventricle width (reflecting atrophy of the thalamus) emerged as the most robust predictor of cognitive deficits, followed by brain parenchymal fraction (ratio of parenchymal to intracranial volume).

In addition to lesion volume and cerebral atrophy, more recent studies have revealed abnormalities in normal appearing white matter (NAWM) and normal appearing grey matter (NAGM), which may not be visible using standard MRI analyses. Using diffusion tensor and magnetization transfer imaging, recent studies have demonstrated that damage to both NAWM and NAGM correlate with deficits in various cognitive domains (Benedict et al., 2007; Akbar et al., 2010).

Despite the moderate to strong associations between structural MR parameters and cognitive deficits in patients with MS, much of the variance in cognitive functioning remains unaccounted for by these measures. In the past decade, there has been an explosion of functional neuroimaging studies, primarily using functional MRI (fMRI) to investigate the neural circuitry underlying MS-related cognitive impairment. The most extensively studied cognitive domain using fMRI is working memory. Using the n-back task to activate the neural systems associated with working memory, fMRI studies have found that MS patients show greater activation in several regions of the working memory neural circuitry compared to healthy controls (Sweet, Rao, Primeau, Durgerian, & Cohen, 2004; Forn et al., 2007). Conversely, another study found decreased activation in these brain regions, but increased activation in regions not typically associated with working memory tasks in patients with RRMS (Wishart et al., 2004). These findings may reflect a certain degree of functional compensation and re-organization in response to structural brain pathology. Similarly, a recent study examining the neural circuitry involved in information processing speed found impaired performance and significantly lower activation in bilateral frontal and parietal regions in MS patients in a modified version of the SDMT (mSDMT; Genova, Hillary, Wylie, Rypma, & DeLuca, 2009). Compared to healthy controls, MS patients also show substantially smaller increases in activation of the working memory neural circuitry as task difficulty increases (Gass et al., 2008), an indication of a ceiling effect in the functional adaptation of the brain due to increased cognitive demands.

The overall findings of functional neuroimaging studies of MS patients during a cognitive challenge suggest: (1) evidence for hyper-activation of regions involved in task performance; (2) evidence for altered patterns of activation suggesting recruitment of alternate neural circuitry not typically activated in healthy individuals; and (3) evidence of a ceiling effect present in the functional adaptation of the brain as task demand increases beyond a certain threshold.

These findings strongly support functional re-organization of the brain in MS patients involving either increased activation of task-relevant neural circuitry or the recruitment of more widespread neural circuits which acts as a compensatory mechanism in the face of MS-induced structural damage. The presence of compensatory strategies may help explain how some MS patients may perform normally on cognitive testing despite the presence of cerebral pathology (Genova et al., 2009). However, there is a threshold of structural damage beyond which compensatory mechanisms no longer apply, indicating that brain plasticity has its limits (Gass et al., 2008). The more complex the cognitive task, or the more extensive the degree of pathological brain changes, the lower the ability of brain plasticity in meeting the challenge of maintaining intact cognition.

1.2.9 Impact of Cognitive Impairment

While cognitive impairment does not affect all patients, the estimated prevalence of 40-60 percent (Rao et al., 1991a; Lyon-Caen et al., 1986) certainly places cognition as one of the most prevalent features of MS, with resultant adverse effects on personal, social, and occupational functioning (Rao et al., 1991b). Deficits in sustained attention and executive functioning have been associated with poorer coping strategies (Goretti, Portaccio, Zipoli, Razzolini, & Amato, 2010), and poor memory and concentration have been found to interfere with everyday functioning (Young, Saunders, & Ponsford, 1976). Patients with cognitive impairment are less likely to engage in social activities, experience more sexual dysfunction, and report greater difficulties with household chores (Rao et al., 1991b).

Cognitive impairment has also emerged as one of the predictors of unemployment in MS patients. Approximately 70-80 percent of MS patients are unable to retain employment (Kornblith, La Rocca, & Baum, 1986; Gregory, Disler, & Firth, 1993). While a multitude of factors including physical disability (Jongbloed, 1996) and depression (Honarmand, Akbar, Kou

& Feinstein, 2010) may account for this, unemployment has also been linked to global cognitive impairment (Rao et al., 1991b), and to poorer performance on measures of information processing speed, attention and verbal fluency (Honarmand et al., 2010).

A series of studies by Schultheis and colleagues have demonstrated the adverse effect of cognitive deficits on driving skills in patients with MS. They found that patients with cognitive impairment had worse performance on driving related tasks (Schultheis, Garay, & DeLuca, 2001) and increased risk of collisions (Schultheis, Garay, Millis, & DeLuca, 2002), compared to healthy controls and MS patients without cognitive deficits. Their most recent study demonstrated that despite variability in the level of neurological disability, most MS subjects demonstrated acceptable driving skills (Schultheis, et al., 2010). However, performance on measures of information processing speed, working memory and visuospatial recall were found to be strong predictors of driving skills and errors on driving simulation tests and collision and violation frequency according to driving records (Schultheis et al., 2010; Kotterba, Orth, Eren, Fangerau, & Sindern, 2003).

1.2.10 Treatment of Cognitive Impairment

Despite the high prevalence and adverse impact of cognitive dysfunction, there are no effective drug therapies to improve cognition in patients with MS. Studies of cognition-enhancing pharmacological agents have focused primarily on acetylcholinesterase inhibitors (AChEIs), such as donepezil, rivastigmine and galantamine, which have been used to treat dementia associated with Alzheimer's disease by augmenting cholinergic activity (McGleenon, Dynan, & Passmore, 1999). While there is no direct evidence for cholinergic deficits in MS patients, cholinergic dysfunction has been found to underlie cognitive deficits in the acute experimental encephalomyelitis model of MS (D'intino et al., 2005). Clinical trials of AChEIs have found improvements in verbal memory and learning in patients treated with donepezil (Porcel & Montalban, 2006; Krupp et al., 2004), but no cognitive effects in those treated with rivastigmine (Shaygannejad, Janghorbani, Ashtari, Zanjani, & Zakizade, 2008) despite findings of other studies showing that the latter drug enhanced prefrontal cortical activation in treated MS patients (Parry et al., 2003; Cader, Palace, & Matthews, 2009).

The use of CNS stimulants to improve cognitive performance is understudied. One study found that a single dose of methylphenidate, a compound that increases levels of dopamine and norepinephrine, improved performance of MS patients on the PASAT (Harel, Appleboim, Lavie & Achiron, 2008). Other agents such as memantine, an uncompetitive NMDA receptor antagonist which has shown efficacy in Alzheimer's disease, have failed to improve cognition in MS patients (Lovera et al., 2010).

The few studies that have examined the effect of immunomodulatory DMDs on cognitive functioning in MS have found mixed results, with the weight of the evidence suggesting some beneficial effects of interferon-B-1b (Pliskin, Hamer, Goldstein, & Towle, 1996; Barak & Achiron, 2002) and interferon-B-1a (Fischer et al., 2000), particularly in those with clinically isolated syndromes and RRMS, but little or no benefits from glatiramer acetate (Weinstein et al., 1999; Schwid, Goodman, Weinstein, McDermott, & Johnson, 2007).

In the absence of effective pharmacological interventions to alleviate cognitive dysfunction in MS, non-pharmacological interventions, such as cognitive rehabilitation, occupational therapy and psychotherapy are of paramount importance. Cognitive rehabilitation includes both compensatory and restorative strategies. Compensatory strategies aim to maximize use of preserved cognitive abilities to aid individuals in coping with areas of deficits. For example, compensatory strategies to assist individuals with memory impairments may include use of memory aids such as notebooks and calendars and computerized memory devices. Restorative strategies introduce a remedial approach aimed at restoring affected cognitive domains. Restorative strategies may include the use of graded practice aimed at improving memory by promoting the functional re-organization of brain networks over time (Messinis, Kosmidis, Lyros, & Papathanasopoulos, 2010).

Evidence for the effectiveness of rehabilitative programs for cognitive dysfunction in MS is mixed, with only a limited number of studies showing improvements in selective attention (Plohmann et al., 1998), mental speed and working memory (Vogt et al., 2009), as well as visual perception (Jonsson, Korfitzen, Heltberg, & Ravnborg, 1993). These findings, should they be replicated in larger samples and prove sustainable in long-term follow-up, are promising. However, the extent to which the cognitive benefits derived from restorative strategies translate into enhanced quality of life remains to be determined.

1.3 CANNABIS

1.3.1 Cannabis Use by the General Population

Cannabis is the most widely used illicit drug in the world. Available data suggest that 3.3 to 4.4 percent of the world population aged 15-64 used cannabis at least once in 2007 (United Nations Office on Drugs and Crime [UNODC], 2009), which far exceeds the global use of any other recreational illicit drug. Prevalence of cannabis use in North America is 10.5 percent, surpassing that of Central and South America, Asia, Europe and most of Africa and use of other recreational drugs in North America (i.e., during the same period, 0.4-1.2 percent reported use of amphetamines in North America; UNODC, 2009). According to the Canadian Addiction Survey conducted in 2004, prevalence of cannabis use among the Canadian population aged 15 and over is at 14.1 percent, with the highest prevalence, 16.8 percent, reported in British Columbia (Adlaf, Begin, & Sawka, 2005).

1.3.2 Cannabis the Plant

Cannabis is the generic name for a variety of preparations derived from Cannabis sativa L. (of the Cannabinaceae family), an annual plant growing widely in temperate and tropical climates of the world. Cannabis contains over 460 known chemical compounds more than 60 of which are cannabinoids (Gaoni & Mechoulam, 1964). The most abundant cannabinoid and the primary psychoactive component in cannabis is Δ-9-tetrahydrocannabinol (THC; Gaoni & Mechoulam, 1964). The other major cannabinoids such as cannabidiol, cannabinol, delta-8-tetrahydropcannabinol, cannabicyclol, cannabichromene, cannabigerol are believed to modify the effects of THC, increasing or decreasing its potency (Abood & Martin, 1992). Cannabidiol, the second most abundant cannabinoid, is psychotropically inactive and is believed to attenuate the effects of THC (UNODC, 2009).

1.3.3 Cannabis as a Drug

The potency of cannabis varies with THC concentration, which in turn depends on a variety of factors including strain, breeding, and the preparation. The three most common preparations of cannabis, herbal cannabis, cannabis resin and cannabis oil, differ in their potency (El Sohly & Ross, 2003; UNODC, 2003).

Marijuana is a tobacco-like herbal preparation of the harvested cannabis plant containing the air dried flowering or fruiting 'tops' and leaves, which are known to contain high THC concentrations. The concentration of THC in marijuana ranges from 0.5 to 14 percent (Fehr & Kalant, 1983a; Jones, 1987). Marijuana is usually smoked in a hand-rolled "joint". A typical joint contains 0.5 to 1.0 g cannabis but the THC concentration can vary between 5 to 150 mg. A small amount of metabolized THC, as little as 2-3 mg, produces a brief euphoria or 'high' for naïve or occasional users (El Sohly & Ross, 2003; UNODC, 2003).

Hashish or cannabis resin refers to the dried resinous secretion and compressed flowers obtained from the cannabis plant. The THC concentration of hashish ranges from 2 to 8 per cent (Fehr & Kalant, 1983a). Hashish can be smoked or orally ingested in food products or beverages (El Sohly & Ross, 2003; UNODC, 2003).

Cannabis oil (or hash oil) is a concentrate of herbal cannabis or cannabis resin. This tar-like viscous fluid is extracted from the cannabis plant or resin and can be smoked (by dropping on tobacco or wiping on the paper) or orally ingested. Hash oil is a highly potent preparation of cannabis, containing between 16 to 60 per cent THC concentration (Fehr & Kalant, 1983a; El Sohly & Ross, 2003; UNODC, 2003).

1.3.4 Routes of Intake

The potency and course of physiological and psychological effects of cannabis also depend on the route of intake. The most common route of cannabis intake is inhalation. Marijuana is most commonly smoked in the form of a cigarette, often combined with tobacco to assist burning. Hashish can also be consumed by smoking as a joint or in a pipe. Marijuana, hashish and hash oil can all be consumed through a water pipe known commonly as a "bong", which minimizes the amount of wasted smoke and enables maximum THC recovery and a more potent effect (El Sohly & Ross, 2003; UNODC, 2003).

Inhalation of cannabis leads to a fairly rapid onset of effects. THC is absorbed from the lungs into the bloodstream within seconds of consumption, reaching maximal brain concentrations within 15 to 30 minutes. This coincides with the period of maximal physiological and psychological effects. Smoking also has a relatively short duration of effect, with plasma THC concentration declining by 50 percent within 15 minutes after consumption. The acute

psychological and physiological effects last approximately two to four hours (Grotenhermen, 2003; Berghaus, Kruger, & Vollrath, 1998)

Hashish and hash oil can also be consumed orally, often in the form of food products or tea. Due to the slower absorption of THC from the gastrointestinal tract, ingestion of cannabis has a slower onset of effects (at least 30 minutes following ingestion compared to seconds following inhalation), delaying peak plasma THC concentrations and maximal psychoactive effects by approximately 1-3 hours but prolonging effects by several hours (6-12 hours following ingestion compared to 2-4 hours following inhalation). Maximal blood concentrations of cannabis components are approximately 20-30 percent of those obtained by inhalation, resulting in a less intense "high" over a longer period of time (Grotenherman, 2003).

1.3.5 Metabolism and Detection

Once THC enters the bloodstream through the lungs (when smoked) or the gut (when ingested), it undergoes a complex series of transformations, producing various active and inactive metabolites. The primary THC metabolites are 11-hydroxy-THC (11-OH-THC), which retains much of the psychoactive property of THC, and its metabolite, 11-nor-9-carboxy-THC (THC-COOH; Huestis, 2007).

Approximately 20 percent of THC is excreted in urine, primarily in the forms of THC-COOH and THC-COOH glucuronide (Huestis, 2007). These metabolites can be detected in urine of cannabis users for over 5 weeks (Harvey, 1999). Quantification of THC from bodily fluids is inherently prone to error given the large variation in the bioavailability of THC from cannabis consumption. Furthermore, given its lipophilicity, THC can be deposited in fatty tissues for days to weeks and released gradually (Nahas, 2001). Therefore, urinary cannabinoid levels do not correlate well with dosage of THC consumed.

1.3.6 The Endocannabinoid System

While early theories on the cellular mechanisms of cannabinoid action held that THC exerts its effects by nonspecifically perturbing all cell membranes, Howlett and Devane used radioimmunoassay techniques to characterize a unique receptor with which THC interacts (Devane, Dysarz, Johnson, Melvin, & Howlett, 1988; Howlett et al., 1990). The existence of

cannabinoid receptors was further confirmed when the gene for the cannabinoid receptor was cloned in the rat (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990) and human brains (Gerard, Mollereau, Vassart, & Parmentier, 1991). Before long, the distribution of these newly identified receptors in the human brain had been mapped (Bidaut-Russell, Devane, & Howlett, 1990; Herkenham et al., 1990).

It is now well recognized that the action of cannabinoids is through receptor-specific mechanisms rather than by membrane-mediated mechanisms as previously hypothesized. The identification of unique receptors by which cannabinoids exert their effects tremendously facilitated the understanding of the biochemical mechanisms underlying the physiological and behavioural effects of cannabis.

To date, two subtypes of cannabinoid (CB) receptors have been identified: CB1 and CB2. CB1 receptors were the first to be discovered and are now believed to be the most widely expressed G-protein coupled receptors in the brain and nervous system but are also expressed in the lungs, liver and kidneys. CB2 receptors were first identified in the spleen, but are also densely expressed in peripheral nerve tissue, as well as hematopoietic and immune cells (Howlett et al., 2002; Munro, Thomas, & Abu-Shaar, 1993). Recent evidence suggests that CB2 receptors are present in astrocytes, microglia, and oligodendrocytes in the brain (Stella, 2004; Maresz, Carrier, Ponomarey, Hillard, & Dittel, 2005; Onaivi et al., 2006).

The endocannabinoid system plays a crucial role in a variety of normal physiological functions including regulation of metabolic function, immune function, nociception and bone mass. CB1 receptors have been shown to play a role in the regulation of synaptic transmission, interacting with various other neurotransmitter systems including dopaminergic, cholinergic, opiate and GABAergic systems (Iversen, 2003). The physiological roles of the CB2 receptor are less clear. Consistent with their peripheral localization, CB2 receptors do not exert psychological and behavioural effects, but are believed to have anti-inflammatory and immunosuppressive roles (Pacher & Mechoulam, 2011).

Identification of a specific cannabinoid receptor on cell membranes pointed to the existence of endogenous cannabinoids (endocannabinoids) that exert their action by selectively interacting with these receptors. The first such molecule to be identified was N-arachidonoylethanolamide

(anandamide). Like THC, anandamide is a lipophilic substance that interacts selectively with cannabinoid receptors although it is 4 to 20 times less potent and has a shorter duration of action than THC (Smith et al., 1994). Shortly after the discovery of anadamide, a more potent naturally occurring agonist of endocannabinoid receptors, 2-arachidonoylglycerol (2-AG), was described (Sugiura et al., 1995).

The anatomical distribution of CB1 receptors in the human brain closely reflects the wide-ranging physiological and psychological effects of cannabinoids. The highest densities of CB1 receptors are found in the basal ganglia, cerebellum, cingulate cortex, hippocampus and regions of the cerebral cortex, in particular the prefrontal cortex, known to subserve cognitive functioning (Glass, Dragunow, & Faull, 1997b; Iversen, 2003). The rewarding effects of cannabis are likely mediated by the nucleus accumbens, which contains a high density of CB1 receptors (Herkenham, Lynn, de Costa, & Richfield, 1991a). The absence of CB1 receptors in the brainstem explains why consumption of high doses of THC is not lethal (Iversen, 2003).

1.3.7 Acute Physiological and Psychological Effects of Cannabis

Cannabis consumption induces a complex array of physiological, psychological and behavioural effects. These effects vary depending on the dose of psychoactive constituents, the route of intake as well as environmental and psychological factors. The short-term physiological effects of cannabis consumption include mild sedation, increased motor activity followed by inertia, problems with coordination, increased appetite, tachycardia, vasodilation, postural hypotension, increased cardiac output, and decreased intraocular pressure (Kalant, 2004).

The most commonly reported acute psychological effects include an altered state of consciousness characterized by euphoria, a sense of well-being, relaxation, distorted perceptions and enhancement of sensory experiences. Together, these experiences constitute what is commonly described as a “high” following cannabis consumption (Tart, 1970). Adverse psychological effects, particularly in response to large doses include confusion, restlessness, anxiety, panic, and depression. Very high doses may also precipitate psychotic episodes featuring hallucinations and delusions (Weil, 1970; Thomas, 1993).

1.3.8 Long-term Physiological and Psychological Effects of Cannabis

Chronic cannabis smokers are more likely to experience symptoms of bronchitis, chronic obstructive pulmonary disease and respiratory infections (Hall & Solowij, 1998). Compared to tobacco users, marijuana smokers have five times the amount of carboxyhemoglobin, inhale three times more tar and have greater retention of tar (Wu, Tashkin, Djahed, & Rose, 1988). There are clinical reports of respiratory tract cancers (Taylor, 1988) in addition to single case reports of lung carcinoma and cancer of the tongue (Caplan & Brigham, 1989) in marijuana smokers. More recent studies however refute the role of cannabis inhalation in chronic obstructive pulmonary disease, lung cancer and head and neck malignancies, even in very long-term, heavy users (Tan et al., 2009; Hashibe et al., 2006)

While marijuana smoking has not been found to induce long-term cardiovascular changes in young, healthy individuals, chronic smoking increases the risk of complications in those with cardiovascular disease (Trouve & Nahas, 1999; Jones, 2002; Sidney, Beck, & Tekawa, 2002).

There is also some indication of increased bacterial and fungal infections associated with cannabis use in patients suffering from Acquired Immune Deficiency Syndrome (AIDS), consistent with the immunosuppressive effects of cannabinoids (Cabral, 2001; Klein, 1999), although there is no evidence that cannabis use leads to the progression of AIDS (Kaslow et al., 1989).

An estimated 5 to 10 percent of cannabis users develop cannabis dependence (Anthony, Warner, & Kessler, 1994), marked by all or some of the following Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria: inability to reduce cannabis intake despite the desire to do so, considerable time spent obtaining cannabis, disruption of social, occupational and personal activities due to cannabis use, using cannabis more often or in larger amounts than intended, continued use despite negative effects, development of tolerance, and withdrawal symptoms. Cannabis withdrawal syndrome, characterized by symptoms such as anger and aggression, decreased appetite, irritability, restlessness, insomnia, and depression (American Psychiatric Association [APA], 1994), has been described in chronic users. Symptoms typically arise within 1 to 2 days and peak between 2 to 6 days following abstinence (Budney, Hughes, Moore, & Vandrey, 2004).

1.4 CANNABIS AS MEDICINE

1.4.1 Medicalization of Cannabis

The medicinal use of cannabis has a rich history spanning several thousand years. The Emperor of China, Shen Nung, was the first to describe the therapeutic uses of cannabis in 2737 BC (Li, 1974). Cannabis was recommended for treating malaria, constipation, headache, fever, venereal disease, rheumatic pain as well as sleep and digestive problems. Its introduction to the West dates back to 1611, when Jameson settlers brought the plant to Virginia for use in hemp production (Belenko, 2000).

In the mid-19th century, William O'Shaughnessy, a British physician working in India, discovered several medicinal uses for cannabis, including as an analgesic, appetite stimulant, antiemetic, muscle relaxant, and anticonvulsant (Mack & Joy, 2001). His publication (O'Shaugnessy, 1839) led to the expansion of the medicinal use of cannabis. Cannabis was entered into the standard pharmaceutical reference works including the United States Pharmacopeia in 1850 (Belenko, 2000), marking the beginning of the modern phase of therapeutic cannabis use.

At the beginning of 20th century in North America, the recreational use of cannabis increased steadily, along with other substances including alcohol and opium. Cannabis was largely neglected in Canadian law until this time. In a book entitled The Black Candle (1922), Canadian Emily Murphy, the first female judge of the British Empire, described the social effects of illicit drug use including marijuana, suggesting that use of any illicit drugs leads to "insanity" and the loss of any sense of "moral responsibility." Quoting the Los Angeles County Chief of Police, Murphy wrote that individuals who use marijuana "become raving maniacs and are liable to kill or indulge in any forms of violence to other persons using the most savage methods of cruelty without… any sense of moral responsibility" (Murphy, 1922). Murphy's sensationalized account of the effects of marijuana as well as the development of aspirin and various other analgesics and sedatives lead to the banning of marijuana under the Opium and Drug Act in Canada in 1923 (Hewitt, 2004).

Renewed interest in the therapeutic use of cannabis began in the 1970s when it was discovered than smoking cannabis alleviates nausea and vomiting in cancer patients undergoing

chemotherapy (Sallan, Zinberg, & Frei, 1975; Chang et al., 1979). Nonetheless, based on the Controlled Substance Act of 1970, marijuana was classified as a Schedule I controlled substance in the United States, although the Act did not restrict its use for legitimate medical and scientific purposes (United States Drug Enforcement Administration, 1970).

Although the unregulated use of cannabis remains illegal under the Controlled Drugs and Substances Act of 1996 and its production is punishable by up to 7 years imprisonment, the Canadian federal government enacted the Marihuana Medical Access Regulations in 2001, granting limited legal access to marijuana for therapeutic use to individuals who demonstrate a medical need. Under the Marihuana Medical Access Regulations, Health Canada allows limited applications for possession of marijuana to those who (a) have a terminal illness, with a prognosis of less than 12 months to live, and (b) those experiencing symptoms associated with a serious medical condition, including but not limited to pain associated with multiple sclerosis, spinal cord injury, AIDS/HIV, severe forms of arthritis and epilepsy. Individuals experiencing debilitating symptoms secondary to other conditions not included above require a declaration from a medical professional confirming that conventional therapies have failed to alleviate symptoms. Authorized patients can obtain marijuana directly from Health Canada, in the form of marijuana seeds and dried marijuana produced by Prairie Plant Systems in Alberta under controlled conditions and containing approximately 12.5% of THC. Health Canada suggests the use of 1-3 grams of cannabis daily regardless of the route of intake. Because it is not an approved therapeutic drug under the Food and Drug Act, medical marijuana is not covered by health insurance plans but costs can be claimed as a medical expense for tax purposes (Health Canada, 2010).

1.4.2 Cannabis-Based Medicines

Anecdotal reports of the therapeutic benefits of cannabis coupled with the identification of the endocannabinoid system have led to the development of a number of pharmaceutical agents aimed at maximizing therapeutic value while minimizing the psychoactive effects of cannabinoids.

Dronabinol (Marinol®), synthetic THC, and nabilone (Cesamet®), a synthetic analog of THC, are two orally administered compounds available in capsule form by prescription in Canada and

the United States for treatment of nausea and vomiting associated with chemotherapy (Tramer et al., 2001; Regelson et al., 1976; Jatoi et al., 2002). Studies have shown some beneficial effects of oral THC for the management of pain in patients with fibromyalgia (Skrabek, Galimova, Ethans, & Perry, 2008) and multiple sclerosis (Rog, Nurmikko, Friede, & Young, 2005).

Cannabis-based extracts have also been developed for medicinal use. Cannador®, available in capsule form, is an extract of the cannabis plant containing THC and cannabidiol in a 2 to 1 ratio. In 2005, Health Canada approved the use of a novel pharmaceutical agent, Sativex®, a cannabis-based extract containing fixed doses of THC and cannabidiol (2.7mg and 2.5mg respectively) and administered as an oromucosal spray, as an adjunctive treatment for management of pain in multiple sclerosis patients (Health Canada, 2010).

1.4.3 Therapeutic Potential of Cannabis

The most unequivocal evidence of the beneficial effect of orally administered cannabinoids (dronabinol or nabilone) comes from the literature on chemotherapy-induced nausea and vomiting. A review of 30 randomized controlled studies showed that oral THC is superior to placebo and other antiemetic agents in treating nausea and vomiting associated with cancer chemotherapy (Tramer et al., 2001). These results however, are based on controlled studies of cannabis-based medicines and do not necessarily extend to inhaled cannabis.

Controlled studies have shown that oral THC stimulates appetite and helps alleviate weight loss in patients with cancer (Regelson et al., 1976; Jatoi et al., 2002) and AIDS (Beal et al., 1995). Randomized trials examining the effects of smoked cannabis have also reported increased caloric intake in HIV-positive patients (Haney et al., 2005; Haney, Rabkin, Gunderson, & Foltin, 2007).

Two studies have found Sativex® to be superior to placebo in alleviating pain associated with rheumatoid arthritis (Blake, Robson, Ho, Jubb, & McCabe, 2005) and neuropathic pain with allodynia (Nurmikko et al., 2007). The results for synthetic cannabinoids (nabilone and dronabinol) have been equivocal, with most studies showing pain relief (Skrabek, Galimova, Ethans, & Perry, 2008; Pinsger et al., 2006, Narang et al., 2008; Berman, Symonds, & Birch, 2004) and others showing no benefits (Frank, Serpell, Hughes, Matthews, & Kapur, 2008; Beaulieu, 2006). Sativex® differs from oral synthetic THC compounds in two important ways

that may influence its therapeutic properties. Firstly, Sativex® contains cannabidiol, which is absent in oral THC compounds. It is plausible that cannabidiol is responsible for the superiority of Sativex® over synthetic THC in alleviating neuropathic pain. In addition, Sativex® is administered in the form of an oromucosal spray, which allows for individualized titration of dosages according to the degree of pain. It may be that the self-titration of Sativex® allows patients to administer higher doses of THC in order to achieve maximal symptom relief. The latter explanation is plausible given that pain relief has been reported at high doses of oral synthetic THC (Noyes, Brunk, Baram, & Canter, 1975a; Noyes, Brunk, Avery, & Canter, 1975b). Inhaled cannabis has also shown benefits in alleviating chronic neuropathic pain (Ware et al., 2010; Wilsey et al., 2008) and pain associated with HIV (Ellis et al., 2009; Abrams et al., 2007) and.

1.5 CANNABIS USE IN MULTIPLE SCLEROSIS

1.5.1 Patterns and Prevalence

Data show that a substantial proportion of MS patients, 36 to 43 percent, have smoked cannabis at some time in their lives (Clark, Ware, Yazer, Murray, & Lynch, 2004; Chong et al., 2006; Page, Verhoef, Stebbins, Metz, & Levy, 2003; Martinez-Rodriguez et al., 2008). Of these, over half reported use of cannabis for the first time after being diagnosed with MS (Chong et al., 2006). An estimated 14 to18 percent of patients continue to use cannabis for medicinal purposes (Clark et al., 2004; Martinez-Rodriguez et al., 2008; Chong et al., 2006). Surveys have also found that patients with MS who use cannabis do so frequently (daily to weekly), and over many years, spending between $50 to $500 dollars monthly on cannabis (Consroe, Musty, Rein, Tillery, & Pertwee, 1997; Page & Verhoef, 2006). Among patients who have never used cannabis, 71 percent indicated that they would do so if it were legal and available by prescription. This suggests that interest in the therapeutic role of cannabis is high and that the primary obstacles are its legal status and limited access (Page & Verhoef, 2006).

Most MS patients who use cannabis report smoking the drug in cigarettes or pipes, although ingestion in food products or beverages is more common among those whose cannabis use is strictly for medicinal purposes compared to recreational users (Martinez-Rodriguez et al., 2008). Use of cannabis among MS patients is associated with being male, tobacco use, being a

recreational user, being in a stable relationship (cohabitating or married), awareness of the potential benefits of cannabis use in alleviating MS symptoms, impaired mobility, and higher self-rated disability levels (Clark et al., 2004; Chong et al., 2006).

In a survey of 175 MS patients, 45 reported having ever used cannabis for recreational and 30 for medicinal reasons (Martinez-Rodriguez et al., 2008). Compared to recreational cannabis users, medicinal users are more likely to be unemployed, use tobacco, score higher on measures of MS-related disability (such as the EDSS), and have a progressive disease course. Medicinal users were also more likely to have MS-related symptoms, to ingest cannabis (recreational users all reported smoking), report symptom alleviation from cannabis, to grow their own cannabis for personal consumption, and to discontinue consumption due to adverse effects. Recreational users were younger at age of first cannabis consumption and were more likely to have used cannabis prior to diagnosis, have higher alcohol consumption, and to use hashish (Martinez-Rodriguez et al., 2008).

1.5.2 Therapeutic Potential of Cannabis in Multiple Sclerosis

Subjective Reports

Early evidence for the purported beneficial effects of cannabis comes from anecdotal and self-report data. Results from the first comprehensive survey of MS patients who use cannabis revealed that approximately 90 percent found amelioration of pain, spasticity, tremor, depression, and anxiety, while over two-thirds reported relief from urinary urgency and undesired weight loss (Consroe et al., 1997). Other studies have confirmed these findings (Clark et al., 2004; Page et al., 2006; Chong et al., 2006; Martinez-Rodriguez et al., 2008).

Less widespread reports of the benefits of cannabis use include alleviation of stiffness/ stress (Clark et al., 2004), relief from bladder and bowel dysfunction (Page et al., 2006), and reduction in dosage of conventional drugs for treating spasticity and pain in nearly half of patients (Clark et al., 2004). Reports of symptom alleviation are however limited only to patients who report smoking cannabis solely for medicinal reasons but not to those who use cannabis recreationally (Martinez-Rodriguez et al., 2008). Notably, over half of medicinal cannabis users reported symptom worsening upon discontinuation, in most cases due to difficulty in obtaining cannabis (Martinez-Rodriguez et al., 2008), although it is unclear to what extent this reflects a withdrawal

syndrome associated with chronic cannabis use rather than exacerbation of MS-related symptoms.

In a qualitative interview study of cannabis use in MS, patients who used cannabis described an overall sense of "peace", "mellowness", relaxation, improved mood, ability to eat and drink, ability to write, enhanced sexual functioning, as well as relief from stress and various MS-related symptoms. Patients also emphasized that their intention was not to achieve a "high" but to minimize symptoms (Page & Verhoef, 2006).

Alongside these perceived benefits, patients have also reported undesired side-effects of cannabis use. The most commonly reported side-effects are sedation, euphoria, laziness and increased appetite (Chong et al., 2006). Patients also report increased problems with balance and fatigue as well as problems with cognition, especially reduced concentration and lucidity and increased forgetfulness (Page & Verhoef, 2006).

Results from Clinical Trials of Cannabis-Based Medicines

Given the plethora of self-report evidence for the benefits of inhaled cannabis in patients with MS, many clinical studies have sought to assess the therapeutic potential of cannabinoids for symptomatic treatment of MS. These studies have focused on synthetic cannabis and cannabis-based medicinal extracts with the aim of maximizing therapeutic potential while minimizing the psychotropic effects associated with inhalation.

Randomized placebo-controlled trials have found subjective improvements in spasticity following treatment with synthetic THC (Ungerleider, 1987; Zajicek et al., 2003) and cannabis extracts containing both THC and cannabidiol (Collin, Davies, Mutiboko, & Ratcliffe, 2007; Wade, Robson, House, Makela, & Aram, 2003; Wade, Makela, Robson, House, & Baseman, 2004; Vaney et al., 2004; Zajicek et al., 2003). In contrast, no studies have found objective improvements on the Ashworth scale, commonly used to assess spasticity (Killestein et al., 2002; Zajicek et al., 2003; Vaney et al., 2004; Wade et al., 2004; Collin et al., 2007). It has been suggested that the discrepancies between self-reported improvements and objective clinical outcomes of spasticity may be due to the relative insensitivity of the Ashworth scale to clinically significant benefits (Pryce & Baker, 2005).

In the Cannabinoids in MS Study (CAMS), the largest randomized placebo-controlled clinical trial of cannabis-based medicines in MS to date, Zajicek et al. (2003) compared the effects of a whole-plant cannabis extract (Cannador®; containing both THC and cannabidiol in capsule form), synthetic THC (Marinol®) and a placebo on spasticity, mobility and other MS-related symptoms in 611 patients over 14 weeks of treatment. They too found no changes on the Ashworth scale in any group although subjective improvements were reported in muscle spasms, pain, sleep quality and general condition by both treatment groups (Zajicek et al., 2003). Of note are improvements on the 10 m walk in the subset of patients receiving Marinol® (Zajicek et al., 2003), a finding that other studies have also reported in those receiving whole-plant cannabis extracts (Vaney et al., 2004; Wade et al., 2003; Wade et al., 2004).

More promising are the results of a 12-month follow-up study of 502 of the 611 patients from the CAMS original sample who opted to continue the treatment (Zajicek et al., 2005). Overall, subjective improvements in spasticity were found in patients receiving THC (Marinol®) and those receiving the cannabis extract (Cannador®). Small but significant improvements were now found on the Ashworth scale in the subgroup receiving Marinol® (Zajicek et al., 2005).

Several studies have reported subjective relief from pain following treatment with cannabis-based medicines (Martyn, Illis, & Thom, 1995; Wade et al., 2003; Zajicek et al., 2003; Svendsen, Jensen, & Bach, 2004; Rog et al., 2005). One study has corroborated these findings with objective measures. Svendsen et al. (2004) used a handheld electronic pressure algometer to examine pain threshold in patients undergoing a placebo-controlled crossover trial of synthetic THC (Marinol®) over a period of 15 to 21 days. They found that in addition to lower patient ratings of pain, patients also showed significantly reduced pressure pain threshold during the active treatment phase (Svendsen et al., 2004).

Several studies have focused on the effects of cannabinoids on urinary and bladder function. The first, a substudy of the CAMS, found significant reductions in urge incontinence assessed using patient diaries in both treatment groups (synthetic THC and cannabis extract) compared to those receiving placebo (Freeman et al., 2006). The second study (Brady et al., 2004) was an open-label trial in which patients received a whole-plant cannabis extract for 8 weeks, followed by a THC-only extract for an additional 8 weeks, both administered in the form of a sublingual spray. Improvements were found in several urinary symptoms including urinary urgency, the

number and volume of incontinence episodes, frequency and nocturia, with the most beneficial effects found during the THC-only phase of the study (Brady et al., 2004). Reduction in the number of daily voids and nocturia were also found by a recent study of MS patients receiving Sativex® (Kavia, De Ridder, Constantinescu, Stott, & Fowler, 2010).

An interesting observation is that the profound subjective benefits of cannabis reported are not generally corroborated by the results of clinical trials. It is important to note however that clinical trials of cannabinoids have focused solely on the oral ingestion of THC or whole-plant extracts. As previously discussed, the pharmacokinetic profile of cannabis varies considerably according to the route of intake. Oral administration of cannabinoids has a slower onset of action, more erratic patterns of absorption and lower peak concentration compared to smoked cannabis which allows for better absorption than oral THC. This may explain why cannabis inhalation provides more rapid symptom relief compared to oral or sublingual routes of administration (Grotenherman, 2003).

Although the therapeutic benefits of cannabinoids in MS have long been speculated, drawing conclusions from the extant clinical trials literature has been challenging. Improvements in study design using more appropriate outcome measures are required, particularly in studies examining spasticity, where the most common primary outcome measure, the Ashworth spasticity scale has been criticized for being relatively insensitive to small but clinically important treatment outcomes (Pryce & Baker, 2005). Furthermore, the treatment duration in most clinical studies, ranging from 1 to 14 weeks, is relatively short and may be insufficient for detecting long-term treatment outcomes. Finally, it would be beneficial to compare the efficacy of cannabis-based medicines to that of standard conventional therapeutic agents to ensure the maximization of therapeutic effects while minimizing undesirable side-effects.

Disease Modifying Effects of Cannabinoids

In addition to their proposed role in alleviating pain, spasticity and other symptoms, cannabinoids are also purported to have a neuroprotective role by influencing T cell balance and cytokine expression (Tanasescu & Constantinescu, 2010). Cerebral insult such as trauma, ischemia and excitotoxic stress, stimulate the synthesis of endocannabinoids by immune cells. In addition, cannabinoid compounds reduce B cell proliferation and immunoglobulin production

(Croxford & Yamamura, 2005; El-Gohary & Eid, 2004) and modulate neurogenesis and neurodegeneration (Tanasescu & Constantinescu, 2010). Animal models of MS have demonstrated the role of cannabinoids in attenuating myelin-specific T cell responses (Croxford et al., 2008). The purported anti-inflammatory, immunomodulating, and neuroprotective roles of cannabinoids are the subject of ongoing research and may provide a promising avenue for therapeutic intervention in diseases like MS.

1.6 NEUROPSYCHOLOGICAL EFFECTS OF CANNABIS

Given the prevalence of cannabis use in society, the potential long-term cognitive effects of cannabinoids are of serious concern. Investigations of the cognitive effects of cannabis in healthy individuals are ridden with methodological weaknesses and ambiguous outcomes, while data are sparse on the adverse effects of cannabis in clinical populations already prone to cognitive dysfunction such as those with MS.

1.6.1 Cannabis and the Brain

Evidence for structural changes in the brains of daily, long-term cannabis users has been inconsistent, with some studies (Matochik, Eldreth, Cadet, & Bolla, 2005; Yucel et al., 2008), but not others (Block et al., 2000a; Tzilos et al., 2005; Jager et al., 2007; Wilson et al., 2000) reporting smaller grey matter volume in cannabis users compared to non-users. Of three studies examining the integrity of white matter tracts, one found significantly reduced mean diffusivity in the anterior portion of the corpus callosum (Arnone et al., 2008), while two others failed to find any differences (Gruber & Yuger-Todd, 2005; DeLisi et al., 2006). These findings suggest that any cognitive changes found in cannabis users are not necessarily linked to regional and global brain volumes.

Functional neuroimaging studies examining *resting* brain metabolism using positron emission tomography (PET) have found evidence of reduced resting state global cerebral blood flow in cannabis smokers following 26 hours to 7 days of abstinence from the drug (Tunving, Thulin, Risberg, & Warkentin, 1986; Lundqvist, Jonsson, & Warkentin, 2001). Reduced regional cerebral blood flow has also been found in the cerebellum (Block et al., 2000b), and prefrontal regions (Block et al., 2000b; Lundqvist et al., 2001). Other studies have found increased resting cerebral blood flow in the right anterior cingulate cortex (Block et al., 2000b), right frontal lobe,

and temporal cerebellum (Sneider et al., 2008), the latter study also noting partial normalization of cerebral blood flow following 28 days of abstinence. There is also limited evidence of lower glucose metabolism in the putamen, precuneous and right orbitofrontal cortex of cannabis users that persists after 12 weeks of abstinence (Sevy et al., 2008).

There is now a sizeable fMRI literature examining regional activation during a cognitive challenge. A review of findings on cannabis users who are neither acutely intoxicated (defined as having smoked cannabis within 12 hours) or making a concerted effort to withdraw from the drug (defined as more than 30 days drug free), reveals a mixed pattern of increased and decreased regional cerebral activations (For a review, see Martin-Santos et al., 2010).

Studies examining performance on tasks of memory and attention have found that compared to non-users, cannabis users showed attenuated activation in the right prefrontal regions (Block et al., 2002; Jager et al., 2007; Chang, Yakupov, Cloak, & Ernst, 2006), bilateral parahippocampal regions (Jager et al., 2007), medial and dorsal parietal cortices (Chang et al., 2006), and medial cerebellar regions (Chang et al., 2006), and greater activation in the posterior cerebellum (Block et al., 2002), and left frontal subgyral, right parietal subgyral and left occipital regions (Chang et al., 2006).

During a task of spatial working memory on which cannabis users performed similarly to controls, Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd (2004) found that cannabis users showed increased activation in the superior, middle and inferior frontal gyrus, right superior temporal gyrus, anterior cingulate cortex (ACC), as well as the caudate and putamen. Jager, Kahn, van den Brink, van Ree & Ramsey (2006) found that the eventual decrease in activation of the left superior parietal cortex observed in non-users over repeated trials was not detected in cannabis users.

Patterns of neural activation during performance of tasks of inhibition have shown decreased activation in the left perigenual ACC and the left lateral prefrontal cortex and increased activation bilaterally in the hippocampi on the Stroop paradigm (Eldreth, Matochik, Cadet, & Bolla, 2004). The latter findings have been partially replicated by Gruber & Yurgelun-Todd (2005) who also found decreased ACC, but increased mid-cingulate activity and more diffuse bilateral activation of the dorsolateral prefrontal cortex.

A feature of many of the fMRI-cognition studies includes a failure to control for one of more of the following factors that potentially could have influenced the results: frequency and extent of cannabis use, serum cannabinoid levels, the presence of co-morbid psychiatric illness, premorbid intelligence with control subjects, duration of abstinence and the age at which the individual first began using cannabis. The last point is underscored by the fact that individuals who commenced cannabis use during adolescence have more profound changes in brain morphology (Pope et al., 2003; Wilson et al., 2000) and earlier age of first cannabis use and greater frequency of use have been associated with greater attenuation of activation in the prefrontal cortex and medial cerebellum (Chang et al., 2006). In addition, regional differences in the neural pathways activated are present in cannabis users even in the absence of neuropsychological deficits (Eldreth et al., 2004; Chang et al., 2006), presumably reflecting a re-modeling of pathways responsible for preserving cognitive performance.

1.6.2 Research Paradigms

There is widespread agreement that the cognitive effects of cannabis vary depending on the period of time since last consumption. In this regard, Pope, Gruber & Yugelun-Todd (2001) have described three general timeframes. The acute effects of cannabis use during the period of intoxication correspond to the time immediately following cannabis consumption through to several hours thereafter during which individuals report experiencing a so-called "high". Although the acute cognitive effects of cannabis intoxication have been widely explored (Solowij, 1998; Ranganathan and D'Souza, 2006), it is unclear whether and to what extent these deficits persist beyond the period of acute intoxication.

The residual effects of cannabis are those that persist beyond the period of acute intoxication. What defines acute intoxication in the literature is somewhat arbitrary with studies variably using cut-off periods ranging from 4 to 24 hours (Leirer, Yesavage, & Morrow, 1991; Barnett, Licko, & Thompson, 1985). Of note however, is that pharmacokinetic studies have shown that the acute cognitive effects of cannabis attributable to the initial rapid rise in serum THC begin tapering off 3 to 5 hours after consumption (Grotenhermen, 2003; Berghaus et al., 1998).

Pope et al. (2001) described the short-term residual effects of cannabis as those detected following a brief period of abstinence ranging from hours to several days. Cognitive effects of

cannabis use detected within this timeframe generally represent potentially reversible alterations and may be attributable to the effect of drug metabolites that continue to linger in the CNS (Pope et al., 2001).

Long-term residual effects refer to abstinence periods exceeding several weeks, at which point cannabinoids are no longer present in the CNS. The cognitive effects of cannabis use detected during this period are attributed to slowly reversible or irreversible CNS alterations, the latter possibly reflecting neurotoxic effects of cannabis (Pope et al., 2001).

1.6.3 Acute Cognitive Effects of Cannabis in the General Population

It is well-established that cannabis intoxication exerts an array of acute cognitive effects such as deficits in choice or complex reaction time (Low, Klonoff, & Marcus, 1973; Moskowitz, Shea, & Burns, 1974; Block & Wittenborn, 1984;1986), information processing speed (Carlin, Bakker, Halpern, & Post, 1972; Vachon, Sulkowski, & Rich, 1974; Heishman, Stitzer, & Yingling, 1989) and divided attention (Moskowitz, Sharma, & McGlothlin, 1972; Casswell & Marks, 1973a; Barnett, Licko, & Thompson, 1985). Impaired memory is the single most commonly reported cognitive effect associated with cannabis intoxication (Ranganathan & D'Souza, 2006), particularly on measures of free recall, where cannabis use leads to fewer words recalled and a greater number of intrusions (Dornbush, 1974; Miller, Cornett, & MacFarland, 1978). It is unclear to what extent impaired recall is due to deficits in memory functions versus deficits in more basic processes such as attention and information processing speed.

The maximum duration of these cognitive deficits following the cessation of cannabis consumption remains unclear. Acute cognitive effects of inhaled cannabis are invariably evident immediately following cannabis use, peak within 15-30 minutes after consumption, taper off within 2-3 hours following cessation of cannabis use (Grotenhermen, 2003), and decline to about zero over 3 to 4 hours after use, although higher doses of THC ($\geq$ 18 mg) continue to affect cognitive performance 5 hours after consumption (Berghaus et al., 1998).

1.6.4 Non-acute Cognitive Effects of Cannabis in the General Population

While controlled studies have shown that cannabis use impairs cognitive functioning when the user is acutely intoxicated, the residual consequences of cannabis use beyond this period are less clear. Early concerns regarding the possible long-term cognitive effects of cannabis arose from clinical observations dating back to the early 1970s, which suggested deficits in judgment, attention, and concentration, as well as confusion, anxiety, depression, apathy, passivity, indifference and slow or slurred speech, in long-term chronic cannabis users beyond the period of acute intoxication, often persisting for months after discontinuation of use (Tennant & Groesbeck, 1972; Kolansky & Moore, 1971;1972). Such reports were limited to those with a history of heavy (daily) cannabis use for more than 1 year (Fehr & Kalant, 1983b), although it is plausible these clinical observations lacked the sensitivity required to detect more subtle impairments associated with lighter cannabis use. These observations raised the possibility that heavy cannabis use may cause adverse effects on brain structure and function, leading to declines in neuropsychological functioning. Despite widespread criticisms of the validity of these clinical observations and their failure to provide evidence of causality, what remained undisputed was their consistency across reports and even various cultures, leading to the explosion of controlled empirical studies investigating the association between cannabis use and cognition using objective neuropsychological measures (Solowij, 1998).

Most controlled studies of the short-term residual effects of cannabis have shown significant deficits on measures of attention and information processing speed (Hanson, et al. 2010; Solowij et al., 2002; Croft, Mackay, Mills, & Gruzelier, 2001; Ehrenreich et al., 1999; Pope & Yurgelun-Todd, 1996; Fletcher et al., 1996; Medina et al., 2007; Wadsworth, Moss, Simpson, & Smith, 2006; Fried, Watkinson, & Gray, 2005; Kelleher, Stough, Sergejew, & Rolfe, 2004), working memory (Hanson et al., 2010; Wadsworth et al., 2006; Pope & Yurgelun-Todd, 1996; Block & Ghoneim, 1993; Fletcher et al., 1996), learning and memory (Hanson et al., 2010; Fried et al., 2005; Solowij et al., 2002; Gianutsos & Litwack, 1976; Rodgers, 2000), reaction time (Ehrenreich et al., 1999), psychomotor speed (Wadsworth et al., 2006), executive functions (Pope & Yurgelun-Todd, 1996), and decision making (Whitlow et al., 2004). One study (Pope & Yurgelun-Todd, 1996) also reported deficits in verbal fluency only in heavy users who also had lower verbal IQ scores. Other studies have failed to find differences between cannabis users

and non-users on measures of attention (Gouzoulis-Mayfrank et al., 2000; Easton & Bauer, 1996; Deif, Sheshai, & Fawzy, 1993; Rodgers, 2000; Carlin & Trupin, 1977; Satz, Fletcher, & Sutker, 1976), learning (Rochford, Grant, & LaVigne, 1977; Gouzoulis-Mayfrank et al., 2000; Brignell, Fletcher, Henry, & Curren, 2000; Hamil, 1996; Carlin & Trupin, 1977; Satz et al., 1976), and psychomotor speed (Rochford et al., 1977; Gouzoulis-Mayfrank et al., 2000; Brignell et al., 2000; Easton & Bauer, 1996).

The literature on the neuropsychological effects of cannabis use is fraught with methodological flaws that render interpretation difficult. Early North American studies were often limited to samples of young, highly educated individuals with a history of infrequent, short-term cannabis use (Grant, Rochford, Fleming, & Stunkard, 1973; Rochford et al., 1977; Hall, Klein, & Waters, 1975; Culver & King, 1974). Furthermore, studies have found that cannabis users score lower on measures of premorbid intelligence (Fried et al., 2005; Lyons et al., 2004; Pope et al., 2003). Given the potential protective roles of age (Hofer & Alwin, 2008), education (Friedman et al., 1986), and premorbid intelligence on cognitive performance, the sampling approach used in these early studies may have led to the exclusion of those who may be more susceptible to the adverse effects of chronic cannabis use.

Several studies have shown that the adverse cognitive effects of cannabis are dose-dependent, with more drastic deficits observed in heavy users compared to occasional or light users (Block & Ghoneim, 1993; Solowij, Michie, & Fox, 1995b; Fried et al., 2005; Pope & Yurgelun-Todd, 1996; Wagner, Becker, Gouzoulis-Mayfrank, & Daumann, 2010). Heavy use has been defined as cannabis use nearly everyday (Block & Ghoneim, 1993; Fried et al., 2005; Pope & Yurgelun-Todd, 1996), or an average of 17.9 days of use per month (Solowij et al., 1995b). Light cannabis use has been more variably defined as less than 5 joints per week (Fried et al., 2005), 0-9 days in the past month (Pope & Yurgelun-Todd, 1996), or an average of 6 days per month (Solowij et al., 1995b). These findings present another challenge to drawing conclusions based on some earlier studies of light cannabis users. While most research focuses on individuals who use cannabis on a daily or weekly basis, some early studies where no cognitive effects were found in cannabis users based their conclusions on samples that used cannabis no more than several times per month (Culver & King, 1974; Hall et al., 1975). Other studies have failed to report the frequency of cannabis use in their sample all-together (Brignell et al., 2000; Lyketsos, Garrett,

Liang, & Anthony, 1999; Bannerjee, Mukhopadhyay, & Shukla, 1997; Elwan et al., 1997; Easton and Bauer, 1996; Carlin & Trupin, 1977; Rochford et al., 1977; Soueif, 1976).

Recent studies have also shown that the degree of cognitive deficits in cannabis users is related to the duration of use (Solowij et al. 2002; Wagner et al., 2010), suggesting that cannabis may have cumulative adverse effects on the CNS, leading to progressive worsening of cognitive functioning with increasing years of use. In light of these findings, it is not surprising that studies of individuals with very brief periods of cannabis exposure, ranging from several months to 3 to 4 years, have failed to show significant cognitive effects (Rochford et al., 1977; Grant et al., 1973; Culver and King, 1974; Weckowicz & Janssen, 1973; Hall et al., 1975; Carlin & Trupin, 1977; Gouzoulis-Mayfrank et al., 2000).

Most controlled studies conducted in the 1970s and 1980s and several recent publications on the topic failed to report the period of abstinence from cannabis at the time of neuropsychological assessment (Weckowicz & Janssen, 1973; Grant et al., 1973; Hall et al. 1975; Soueif, 1976; Satz et al. 1976; Rochford et al., 1977; Deif et al., 1993; Elwan et al., 1997; Bannerjee et al., 1997; Kelleher, Stough, Sergejew, Rolfe, 2004; Wadsworth et al., 2006). This poses a further challenge to the interpretation of these findings because it is unclear whether cannabis users were examined in an acutely intoxicated state or following short- or long-term abstinence.

Evidence for the long-term recovery of cognitive functions following a prolonged period of abstinence has been mixed with some studies reporting some persistent cognitive deficits (Hanson et al., 2010; Medina et al., 2007; Rodgers, 2000; Solowij et al., 2002) while others suggesting complete recovery of cognitive functions following approximately one month of abstinence (Pope et al., 2001; Schwartz, Gruenewald, Klitzner, & Fedio, 1989; Ehrenreich et al., 1999; Fried et al., 2005). In a comprehensive study examining the short- and long-term residual effects of cannabis, Pope and colleagues (2001) compared the neuropsychological performance of 63 subjects who had been using cannabis for an average of 19 years with that of 45 former cannabis users and 72 controls with a limited history of cannabis use, at three time points following discontinuation of cannabis use: Day 0, Day 7, and Day 28. Former heavy users showed no significant deficits on any neuropsychological measures on Day 0 compared to non-user controls. Current heavy users on the other hand, showed deficits on verbal memory on Day 0 and Day 7 but no such deficits on Day 28. These findings suggest that while residual

neuropsychological deficits are present within the first few days or weeks after discontinuation of cannabis use (Day 0 and 7 in this study), performance "normalizes" following an extended period of abstinence (Day 28). It is plausible that long-term residual cognitive deficits may be domain-specific. For instance, Hanson et al., (2010) found recovery of function in verbal learning and working memory but persistent deficits in attention in adolescent cannabis users following three weeks of abstinence. Although the precise factors that may predispose some individuals to long-term cognitive effects of cannabis remain to be elucidated, these findings point to the importance of differentiating between the short-term residual effects of cannabis, which are observed after a brief period of abstinence, and the long-term chronic effects, which are long-lasting and possibly irreversible neurotoxic effects of cannabis exposure that persist after the body is cleared of cannabinoid residues (Pope et al., 2001).

It is evident that drawing conclusions from the extant literature is challenging due to methodological limitations, such as variability in sample characteristics, particularly age and education, period of abstinence, as well as frequency and duration of cannabis use. Nonetheless, several generalizations can be made regarding the non-acute effects of cannabis on cognition in healthy individuals. First, it is reasonable to conclude that heavy, prolonged cannabis use is associated with deficits in selective cognitive domains, particularly in immediate and delayed memory, information processing speed, working memory, attention, and executive functioning, that persist beyond the period of acute intoxication. Second, gross cognitive dysfunction and dementia associated with cannabis use in the absence of other dementia-related risk factors are uncommon. Therefore, long-term chronic cannabis users can generally function well in everyday routine or automatic activities but may experience deficits in cognitively demanding situations requiring rapid processing of novel information, complex executive functions, and memory and learning (Solowij, 1998).

1.6.5 Cognitive Effects of Cannabis in Patients with Multiple Sclerosis

The literature on the cognitive effects of cannabis on cognition in MS patients is sparse. Of published clinical trials examining the efficacy and side-effects of cannabis-based medicines in MS, only five have addressed the cognitive effect of cannabinoids (Aragona et al., 2009; Rog et al., 2005; Wade et al., 2004; Vaney et al., 2004; Langdon et al., 2003).

The only clinical trial focusing exclusively on the cognitive and psychopathological effects of cannabis-based medicines (Aragona et al., 2009) reported greater interpersonal sensitivity, aggressive tendencies and paranoiac features in the treatment group receiving Sativex® at dosages higher than those typically used in therapeutic settings. However, cognition, as assessed by the PASAT, was not affected by the treatment.

Four other clinical trials included cognition as a secondary outcome measure. Of these, one found reduced verbal learning and memory in those receiving cannabinoids for 14 weeks (Langdon et al., 2003), whereas two found no deleterious effects of cannabinoid treatment on measures of information processing speed (Vaney et al., 2004) and short orientation memory and concentration (Wade et al., 2004). The fourth study found that slight improvements in verbal memory in the placebo group over the course of the study (attributed to practice effects) were not observed in those receiving cannabinoid treatment for 4 weeks (Rog et al., 2005).

Given that these trials of medicinal cannabinoids have examined only therapeutic, self-titrated dosages for brief durations ranging from 2 to 14 weeks, it is not surprising that these studies have failed to show extensive deleterious effects on cognition. Furthermore, the pharmacokinetic properties of cannabinoids differ depending on the route of intake. Therefore, the absence of cognitive effects following administration of cannabis-based medicines does not necessarily extend to inhaled cannabis use.

In the only study to date investigating inhaled cannabis, Ghaffar and Feinstein (2008) found that 10 MS patients out of a sample of 140 consecutive clinic attendees reported inhaling cannabis within the last month. These subjects were matched to 40 non-users on age, sex, years of education, and EDSS, duration of MS symptoms and disease course. All subjects completed the Neuropsychological Battery for MS which consists of four tests: the Selective Reminding Test as a measure of verbal memory, the 7/24 Spatial Learning Test as a test of non-verbal memory, the PASAT as a marker of information processing speed and working memory, and the COWAT as a probe of verbal fluency. In addition subjects completed a computerized, in-house derived version of the SDMT. The most significant findings to emerge were that cannabis users had greater impairment on the SDMT with their performance times approximately 50 percent slower than non-users. Cannabis smokers also had significantly more lifetime psychopathology (mainly depression) as elucidated with the Structured Clinical Interview for DSM-IV. This pilot

data provided the first preliminary data suggesting that inhaled cannabis could have deleterious cognitive consequences in patients with MS (Ghaffar & Feinstein, 2008). However, the study suffered from a small sample size, a limited neuropsychological battery, and the absence of urinalysis confirming cannabis use.

1.7 THE PRESENT STUDY

Cannabis use by patients with MS is not only prevalent, but also chronic and under-researched. Rising interest in the therapeutic use of cannabinoids to alleviate MS symptoms necessitates in-depth assessment of the side-effects of cannabis in this group. Given that MS itself leads to significant cognitive impairment in nearly half of patients, any drug that can add to this burden gives cause for concern.To date, only one study has investigated the cognitive effects of inhaled cannabis in patients with MS (Ghaffar & Feinstein, 2008). While informative, this study suffered from various methodological limitations, including a small sample size, a limited cognitive battery, and no confirmation of cannabis use. A prospective exploratory study was therefore designed to examine the non-acute cognitive effects of inhaled and ingested cannabis in patients with MS using a comprehensive neuropsychological battery as well as urinary confirmation of cannabis use, while controlling for potential confounding demographic and disease-related variables. In the general population literature, many studies have failed to take into account the period of abstinence from cannabis. The present study was designed to specifically assess the short-term residual effects of cannabis following a brief period of abstinence, but while cannabinoids can still be detected in the body. Based on the findings of previous cognitive studies in cannabis users and patients with MS, it was hypothesized that:

(1) Patients with MS who use cannabis will have poorer performance on measures of verbal memory, information processing speed/attention, and executive functioning than non-users.

(2) Patients with MS who use cannabis will be more likely to have global cognitive impairment compared to non-users.

(3) Among patients with MS who use cannabis, urine cannabinoid levels, age of onset of cannabis use, and duration of use will be correlated with global cognitive impairment.

CHAPTER 2: METHODS AND MATERIALS

2.1 SAMPLE SELECTION

Subjects with a diagnosis of MS according to the McDonald criteria (McDonald et al., 2001) were enrolled from MS Clinics at St. Michael's Hospital and Sunnybrook Health Sciences Centre and through referrals from community neurologists between February 2009 and April 2010. Only those between the ages of 18 and 65 were enrolled. Subjects older than 65 years of age were excluded in order to partially avoid the potential confounding effects of cognitive decline associated with advanced age (Hofer & Alwin, 2008). Exclusionary criteria included: history of traumatic brain injury, psychotic illness, concurrent neurological diseases (e.g., traumatic brain injury, cerebrovascular accident) other than MS, neuropsychological testing within the last year (in order to avoid possible practice effects on cognitive test performance), poor visual acuity (defined as less than 20/70 corrected, both eyes, based on recommendations by Benedict et al., 2002), and inability to provide informed consent.

For the cannabis sample, only those who reported smoking or ingesting cannabis in the last 5 weeks, and whose urine tested positive for cannabinoids but no other illicit drugs on the day of assessment were included. Subjects who reported cannabis use less than 12 hours prior to testing were excluded in order to avoid assessing those who were acutely intoxicated.

For the control (non-user) sample, only patients who reported no history of regular cannabis use and had urine that tested negative for cannabinoids and other illicit drugs were enrolled. A remote history of occasional teenage use was not an exclusionary factor. Non-users were group-matched to cannabis users on age, sex, education, premorbid intelligence, level of disability, as well as disease course and duration.

Eligibility was determined by administering a pre-screening questionnaire assessing the inclusionary and exclusionary criteria (Appendix A). Patients deemed eligible to participate in the study based on the pre-screening survey were invited to take part in the study.

2.2 INSTRUMENTS AND MEASURES

2.2.1 Socio-Demographic and Disease-Related Data

Demographic variables, namely age, sex, education, marital status, alcohol consumption, and employment status, were collected from each patient. Disease-related variables including disease course and duration, and current medications, were obtained from each patient (Appendix B). Disease course and neurological disability according to the Expanded Disability Status Scale (EDSS; Kurtzke, 1983) were recorded from patients' medical charts within 6 months prior to the day of neuropsychological assessment. Vision was assessed using the Rosenbaum Pocket Screener.

2.2.2 Cannabis Use

History of cannabis use was recorded for all patients. Current cannabis users were also asked to indicate the age of onset, frequency of cannabis use, and mode of intake. Reasons for cannabis use were recorded according to three categories: medicinal, recreational or a combination of the two (Appendix B).

2.2.3 Urinalysis

All urinalysis was conducted at The Hospital for Sick Children, Department of Paediatric Laboratory Medicine/ Toxicology Laboratory. A urine sample was collected from each patient in a 3 oz. container. Broad-spectrum analysis was conducted to determine the presence of the following substances: cannabis, cocaine, opiates, amphetamines, and PCP. The presence of all drugs except barbiturates and cannabinoids was determined using HPLC/ tandem mass spectrometry (LC/MS/MS), a method that combines chromatographic separation and MS/MS analysis to identify drugs in biological fluids. Barbiturates and Cannabinoids were analyzed by Enzyme Immunoassay (EMIT, Syva, Siemens Healthcare Diagnostics). The Cannabinoid assay detects 11-nor-9-carboxy-Δ-9-tetrahydrocannabinol (THC-COOH) and THC-COOH glucuronide in urine. These levels are combined to provide a composite score.

2.2.4 Psychiatric Assessment and Fatigue

Structured Clinical Interview for the DSM-IV

Lifetime history of major depressive episodes and anxiety disorders was established using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; APA, 1994). The SCID-I is a semi-structured interview used for diagnostic evaluation for of the major DSM-IV Axis I disorders. Only the Mood Episodes and Anxiety Disorders modules were administered.

Hospital Anxiety and Depression Scale

To quantify the extent of current symptoms of depression and anxiety, subjects completed the 14-item Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Originally developed to assess mood and anxiety in general hospital patients, one of its primary features is its lack of reference to physical symptoms (i.e., low energy, changes in appetite, sleep problems). Therefore, it is ideal for use in patients with a physical illness because it eliminates possible confounding effect of symptoms such as fatigue, appetite loss and sleep disturbances, which may be attributable to MS itself. The scale has been widely used in MS research and has been validated for use in patients with MS (Honarmand & Feinstein, 2009).

Seven items on the HADS assess depressive symptoms. Of these, five are primarily related to mood (e.g., sadness, ability to enjoy activities), one addresses concerns about one's appearance and another "feeling slowed down." The remaining seven items address common features of anxiety (e.g., tension, restlessness) as well as autonomic symptoms (e.g., panic and feeling butterflies in the stomach). Each item was rated by the patient on a 4-point scale ranging from 0 to 3 according to how the patient has felt during the last week. Total scores range from 0 to 21 on each subscale, with a higher score indicative of higher levels of depression or anxiety depending on the subscale.

Modified Fatigue Impact Scale

The Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994b), a 21-item self-report scale, was administered to quantify the impact of fatigue on physical, cognitive and psychosocial functioning. The MFIS has high reliability and validity as an evaluative tool for the impact of fatigue on patients with MS (Gruszczak, Bartosik-Psujek, Pocinska, & Stelmasiak, 2009). For

each item, subjects were asked to indicate the impact of fatigue on the given activity on a scale of 0 to 4. Total scores range from 0 to 84, with higher scores indicating a greater impact of fatigue on daily activities.

2.2.5 Neuropsychological Assessment

Premorbid Intelligence

The American National Adult Reading Test (ANART; Nelson, 1982) was used to obtain an estimate of premorbid intellectual functioning. The ANART assesses vocabulary as a proxy for premorbid intelligence and has been shown to be a valid and stable estimate of premorbid verbal IQ (Crawford et al., 2001; Moss & Dowd, 1991). Each subject was presented with a sheet of paper (8.5 x 11 in.) containing 50 phonologically irregular words (e.g., pint, gauge, meringue). Subjects were asked to read the list of words, pausing after each word until the examiner says "next". Accurate pronunciation of words in this test requires prior familiarity with the words as phonological decoding and guessing are unlikely to result in an accurate response. Subjects were awarded one point for each correctly pronounced word. The number of incorrectly pronounced words (errors) was tabulated and the corresponding verbal IQ score was recorded for each patient.

Minimal Assessment of Cognitive Function in Multiple Sclerosis

To assess cognitive functioning, all patients were administered the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2002). This 90-minute comprehensive battery includes 7 tests measuring 11 cognitive indices and assesses the domains of cognitive functioning most commonly affected in MS. These include: verbal and visual learning and memory, verbal fluency, visuospatial processing, executive functioning, information processing speed, working memory and attention.

California Verbal Learning Test II

The California Verbal Learning Test II (CVLT-II) measures the ability to encode, store, retain and retrieve verbal information (Delis, Kramer, Kaplan, & Ober, 2000). The first component of the test consisted of 5 trials of Immediate Free Recall, during which a list of 16 words (List A) was read to the subject at a rate of one word per second. The word list included items belonging

to four different categories (vegetables, animals, furniture and modes of transportation) presented in a pseudo-random order. The subject was then asked to recall the items from the list in any order while responses were recorded by the examiner. Then the examiner read the same list to the subject, and asked the subject to recall the entire list again. This was repeated for a total of 5 trials. Next was the Interference Trial, in which the examiner read a list of 16 different words (List B) and asked the subject to recall words only from the second list. Then, the subject was again asked to recall words from List A without re-exposure to the list (Short Delay Fee Recall trial). Next, subjects were asked to recall words from List A belonging to each of the four categories (Short Delay Cued Recall; e.g., "tell me all the words from the first list that are vegetables"). Provision of the category to the subject is expected to serve as a cue to aid in recall. Following a 20-minute delay during which other cognitive tests were completed, the subject was asked to recall all the words from List A again without re-exposure (Long Delay Free Recall) followed by a Long Delay Cued Recall trial. A Recognition Trial completed the test. Here, subjects were presented with a list of 32 words, 16 of which belonged to List A (targets) and 16 belonged either to List B or were not previously read (distracters).

Primary outcome measures include Immediate Free Recall (sum of words from List A recalled on the 5 acquisition trials) and Long Delay Free Recall (the number of words from List A recalled after a 20-minute delay). Secondary outcome measures included the total number of correct responses on the Intrusion Trial (List B Recall), Short Delay Free Recall, Short Delay Cued Recall, Long Delay Cued Recall, and the number of Hits (accurate recognition of targets) and False Positives (false recognition of non-targets) on the Recognition Trial. The total number of intrusions across all trials, which is indicative of the ability to discriminate between relevant and irrelevant responses, as well as perseverations (repetitions) associated with the ability to inhibit previous responses, were also recorded. Standardized scores adjusted for age, sex and education were calculated by the CVLT-II software (Delis et al., 2000).

Brief Visuospatial Memory Test Revised

The Brief Visuospatial Memory Test Revised (BVMT-R) is a test of short-term and long-term visuospatial memory and learning (Benedict, 1997). During the Immediate Recall Trials, subjects were presented with a display of six figures, arranged in a 2 x 3 matrix on a sheet of paper (8.5 x 11 in.) for 10 seconds and were then instructed to draw the figures in their correct

location from memory on a blank sheet of 8.5 x 11 in. paper. Subjects were provided as much time as they needed to reproduce the display. Subjects were re-exposed to the display for 10 more seconds and asked to re-draw all the figures again. This was repeated for a total of three trials. For each figure, subjects were awarded 1 point for correctly reproducing the figure and 1 point if the figure was correctly located relative to the other 5 figures. Therefore, each trial was awarded a maximum of 12 points. The sum of the scores on each of the 3 trials constituted the overall score for Immediate Recall. Subjects were then told "try not to forget the figures as I may ask you to remember them again later." Following a 20-minute delay during which other cognitive tests were administered, subjects were asked to draw all the figures without re-exposure to the initial display (Delay Recall Trial). As before, 1 point was allotted for correct reproduction of the figure and another point for correct location, for a maximum of 12 points for the Delay Recall Trial. This was followed by the Recognition Trial, in which subjects were presented with 12 items (6 targets and 6 distracters), each on a separate page, and were asked to indicate whether or not each figure appeared on the display they viewed earlier. Throughout this test, subjects with motor impairments that limited their ability to draw were offered the necessary assistance by the examiner in the form of holding the paper steady or helping to hold their hand steady while drawing the figures.

Primary outcome measures included Immediate Recall (sum of scores on the 3 Immediate Recall Trials) and Delay Recall (total score on the Delay Recall Trial). The BVMT-R Learning Score, a measure of learning over successive trials, was calculated by subtracting the raw score of Trial 1 from the higher value of Trial 2 or Trial 3 score. Percentage of previously learned information retained across delay ([Delayed recall / higher of Trial 2 and 3] x 100) was also calculated. On the BVMT-R recognition trial, the number of Hits (correctly recognized targets out of 6) and False Alarms (falsely recognized non-targets out of 6) were recorded. Demographically corrected normative data are available for various age groups (Benedict, 1997).

Controlled Oral Word Association Test

The Controlled Oral Word Association Test (COWAT) is a test of phonemic fluency and retrieval, assessing initiation, simultaneous processing of multiple rules, and systematic retrieval of words (Benton & Hamsher, 1989). Subjects were instructed to generate as many words as

they can that begin with a particular letter of the alphabet in 60 seconds, while refraining from: (1) using proper nouns (e.g., if given the letter N, proper nouns such as "Nancy" or "Norway" cannot be used), (2) counting numbers (e.g., ninety, ninety-one), and (3) grammatical variants of a word already given (e.g., if the word "nip" was previously given, subject must not alter the ending and also say "nips", "nipped", "nipping"). All responses were transcribed by the examiner. The total number of correct responses that obey the above rules across the 3 trials (letters F, A, and S) was used as the primary outcome measure. Secondary outcome measures included the total number of intrusions (words that do not obey the rules) and perseverations (repetitions) across the 3 trials. Normative data are available for males and females aged 17 to 80 (Delis, Kramer, Kaplan, & Ober, 1987).

Judgment of Line Orientation

The Judgment of Line Orientation (JLO) was designed to assess visuospatial perception (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). For this study, Form H of the JLO was administered to all subjects. Subjects were presented with a multiple choice response card, presented in the lower part of the test booklet, which consisted of an array of 11 lines (3.8 cm each, labeled "1" through "11") oriented from 0 to 180 degrees at 18 degree intervals. The test stimuli, located in the upper part of the booklet, consisted of two partial lines (1.9 cm), each corresponding to the orientation of one of the lines in the multiple choice array but representing only a segment of the complete line. Subjects were instructed to identify the orientation of each test item by matching it to the array of lines presented in the lower part of the booklet. Following 5 practice items, 30 test items, each consisting of two partial lines, were administered in ascending order of difficulty. The number of completely correct responses to the 30 test items (with corrections for the influence of age and sex: +2 points for women; +1 point for individuals between 50 and 64 years of age) was used as the primary outcome measure. Normative data adjusted for age and sex have been published (Benton et al., 1994).

Sorting Test

Part of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001), the Sorting Test taps into various components of executive functioning including initiation of problem-solving behaviour, concept-formation, verbal and non-verbal problem-

solving skills, abstraction, ability to transfer concepts into action, and response inhibition. For this study, only the Free Sort condition of this task was administered as recommended by Benedict et al. (2002). Subjects were presented with a set of six cards, each displaying a word and containing various perceptual features (e.g., colours, shapes, stripes…etc.). Subjects were instructed to sort the cards into two groups of three according to a common feature and to provide a description of the concept or rule used to generate each group. Two different trials using different sets of cards (Card Set 1 and 2) were used in this study. Verbal responses were transcribed by the examiner and scored according to previously established guidelines (Delis et al., 2001). Outcome measures included the sum of the correct sorts generated and the description scores across the two trials. Standardized scores adjusted for age and education are available in the D-KEFS manual (Delis et al., 2001).

Paced Auditory Serial Addition Test

The Paced Auditory Serial Addition Test (PASAT) is a measure of information processing speed, sustained attention and working memory (Gronwall, 1977). In this task, subjects were presented with a series of single digit numbers at a rate of one digit per 3 seconds (PASAT-3) and 2 seconds (PASAT-2) on an audiotape. Subjects were instructed to add each two consecutive numbers spoken in a row and verbalize the answer (e.g., when you hear "5, 7, 3, 2", you would add each two consecutive digits spoken in a row and respond, "12, 10, 5"). Subjects were forewarned that this test is challenging and that if they "fell behind" and skipped a few responses, they should "jump back in" by listening for the next two digits spoken in a row and providing the answer. They were also told that the tape would not be stopped once the test began. A short practice trial preceded each 60 item test. Primary outcomes measures were the total number of correct responses (out of a total of 60) on the two versions.

Symbol Digit Modality Test

The Symbol Digit Modality Test (SDMT) is a highly sensitive measure of information processing speed, attention and working memory (Smith, 1982). Although the test is designed to allow for written or oral responses, only the oral version of this test was administered in order to minimize the effects of motor deficits. This task involved the presentation of an 8.5 x 11 in. page at the top of which was a key displaying a series of nine digit-symbol pairs. The remainder

of the page contained a pseudo-randomized sequence of the symbols. Subjects were instructed to verbally indicate the digit matching each symbol according to the key at the top of the page as quickly and accurately as possible until they were asked to stop. This can be accomplished by visually scanning the key to locate the correct symbol-digit pairing or by recalling the digit-symbol pairings from their previous inspection of the key. A brief practice trial preceded the test, during which time subjects were given feedback if they provided inaccurate responses. During the test, the examiner timed the performance of each subject for 90 seconds and noted any inaccurate responses. The outcome measure was the number of correct responses in 90 seconds.

Cognitive Impairment

Impaired performance on each of the 11 cognitive indices was defined as scoring 1.5 standard deviations or more below published normative values based on age, sex and education, as necessary. Global cognitive impairment on the MACFIMS was defined as impaired scores on 2 or more of the 11 cognitive indices (Benedict et al., 2006).

2.3 PROCEDURES

All testing was conducted at Sunnybrook Health Sciences Centre. To minimize the impact of fatigue on cognitive performance, sessions were scheduled at times of the day when the patient reported the least amount of fatigue and other MS-related symptoms. After providing written informed consent, subjects took part in a testing session lasting approximately 3 hours.

For each task, subjects were provided with instructions and asked if they understood the task prior to commencing. Subjects were provided optional breaks throughout the session. It was ensured that the administration of the neuropsychological tests with defined inter-trial intervals (e.g., CVLT-II and BVMT-R Delayed Recall Trials) were not influenced by this arrangement.

Following the testing session, participants were remunerated for transportation costs and any questions regarding the study were answered. All participants were given the option of receiving feedback regarding their neuropsychological performance by making an appointment to meet with a neuropsychiatrist, to whom the results were forwarded with the patient's permission.

Alternatively, patients were given the option to have their neuropsychological results forwarded to their family physician or neurologist.

2.4 ETHICS APPROVAL

Ethics approval for the study was obtained from Research Ethics Boards at Sunnybrook Health Sciences Centre and St. Michael's Hospital, both affiliated with the University of Toronto. All participants provided written informed consent prior to participating in the study (Appendix C).

2.5 STATISTICAL ANALYSES

All data were analyzed statistically using the Statistical Package for the Social Sciences (SPSS for Windows) version 16.0. Groups were compared on the socio-demographic and disease-related variables using Student's t-tests for continuous and chi-squared (X^2) analysis for categorical variables.

Primary analysis included between-group comparisons with t-tests for continuous and X^2 analyses for ordinal data to determine whether there are differences between cannabis users and non-users on the cognitive and psychiatric measures. The Mann-Whitney U test was used for non-normally distributed variables. Post-hoc statistical power analysis and effect size calculations (Cohen's *d*) were conducted using the G*Power software for each of the 11 cognitive indices.

Further cognitive comparisons between cannabis users and non-users were performed with a series of linear regression analyses, with each of the 11 cognitive indices as the dependent variable and cannabis use (Group) as the independent variable. Group was entered as the first covariate and confounding variables, namely age, sex, education, EDSS, alcohol consumption, depression, anxiety and fatigue were entered sequentially into the analysis as covariates. The change in the Group coefficient was calculated with the addition of each covariate. Only covariates that changed the Group coefficient by 10 percent or more were retained in the final model for each cognitive measure. Duration and frequency of cannabis use was not included as covariates as they would only apply to the cannabis group.

Similarly, binary logistic regression analysis was conducted to explore the effect of cannabis use on global cognitive impairment after controlling for the aforementioned covariates. As before,

only covariates that changed the Group coefficient by 10 percent or more were retained in the final model for global cognitive impairment.

Pearson's correlations were conducted to explore whether age of onset of cannabis use, duration of cannabis use and urine cannabinoid levels were correlated with global cognitive impairment as had been hypothesized. X^2 analysis was used to determine whether global cognitive impairment was associated with the duration of abstinence from cannabis (12-24 hours vs. greater than 24 hours).

CHAPTER 3: RESULTS

3.1 SAMPLE CHARACTERISTICS

3.1.1 Entire Sample

A total of 38 MS patients who reported smoking or ingesting cannabis on a regular basis were recruited. Of these, 13 were excluded from analysis for failing to meet the inclusionary/ exclusionary criteria. Specifically, 4 subjects tested negative for cannabinoids on the day of the testing; 7 subjects were acutely intoxicated (reported having smoked cannabis < 12 hours prior to the session); one subject failed to complete testing; and one subject did not have a diagnosis of MS. The final cannabis group consisted of 25 subjects (11 females). Twenty-five non-cannabis using MS patients (12 females) were selected from a larger sample of 38 cannabis naïve users such that they matched the cannabis using sample on age, sex, level of education, premorbid intelligence based on the ANART, EDSS score, as well as disease course and duration.

The mean age of the entire sample was 43.60 (SD: 10.7). Thirty-three patients (66.0%) were married or cohabitating and 21 (42.0%) were employed. Patients had received an average of 14.0 years (SD: 2.8) of education. Average disease duration was 12.1 years (SD: 9.4). The breakdown of disease course was: relapsing-remitting 72.0%; secondary progressive 18.0%; primary progressive 10.0%. The median EDSS score was 3.0 (mean: 3.32, SD: 2.39, range: 0-8.5). Twenty patients (40.0%) were taking disease-modifying drugs. Four subjects had taken steroids within the last 3 months. Patients reported consuming an average of 3 alcoholic beverages per week (median: 2.0, SD: 3.3, range: 0-12).

3.1.2 Comparison Between Cannabis Users and Non-users

Comparisons between cannabis users and non-users on socio-demographic and disease-related variables are presented in Table 1. There were no statistically significant group differences for age, sex, education, premorbid intelligence, EDSS score, disease course, disease duration, marital status, and use of disease-modifying drugs. Cannabis users were twice as likely as non-users to be unemployed. Cannabis users also reported slightly higher alcohol consumption compared to non-users, although this difference did not reach statistical significance (Table 1).

Table 1. Comparison of cannabis users and non-users on demographic and disease-related variables.

Sample	**Cannabis users**	**Non-users**	**t or x^2**	***p***
Variable				
Age*: mean (SD)	43.6 (11.7)	43.6 (9.8)	t = 0.000	1.000
Sex*: F/M	11/14	12/13	x^2 = 0.081	0.777
Education* in years (SD)	13.5(2.8)	14.6(2.8)	t = -1.482	0.145
ANART*: mean (SD)	108.6 (9.7)	112.5 (7.1)	t = -1.581	0.120
Employment status: n (%) currently employed	7 (28.0)	14 (56.0)	x^2 = 4.023	0.045
Marital status: n (%) married/ common-law	16 (64.0)	17 (68.0)	x^2 = 0.089	0.765
Disease duration* in years, mean (SD)	11.4 (7.6)	12.7 (11.0)	t = -0.479	0.634
Disease course* (n)				
Relapsing-Remitting	17	19	x^2 = 0.422	0.810
Primary/ Secondary Progressive	3/5	2/4		
EDSS*: median (range)	3.0 (0-8.5)	2.0 (0-8.0)	t = 1.186	0.241
Disease-modifying drugs: n (%)	11 (44.0)	9 (36.0)	x^2 = 0.333	0.564
Alcohol: number/week, median (range)	2.5 (0-12)	1.0 (0-8)	t = 1.870	0.068

ANART: American National Adult Reading Test; EDSS: Expanded Disability Status Scale

* Groups were matched on this variable.

3.2 CANNABIS USE

The average age of onset of cannabis use was 17.0 (median: 15.0, SD: 6.6, range: 13-47) and the average duration of use was 26.6 years (median: 31.0, SD: 12.1, range: 1-41). Eighteen subjects (72.0%) used cannabis on a daily basis, 6 (24.0%) used weekly, and one reported bi-weekly use. Most cannabis users (n = 24) reported inhalation (smoking or vaporization) as the primary route of intake while one reported consumption of food products containing cannabis.

Three subjects had tried medicinal forms of cannabis such as Sativex® or Marinol® in the past, but none had used cannabis-based medicines in the past year. Eight subjects (32.0%) reported using cannabis for medicinal reasons, 3 (12.0%) for recreational reasons, and 14 (56.0%) for a combination of the two.

Mean level of urine cannabinoid metabolites was 174.4 ug/L (SD: 40.8, range: 61 to ≥200) and the broad-spectrum drug screen indicated that no subject had used any illicit drugs other than cannabis. The period of abstinence from cannabis use before testing ranged from 12 hours to 14 days with most (n = 18) reporting their last use on the evening prior to testing.

Among non-cannabis users, 9 subjects (36.0%) reported previous use of cannabis not exceeding occasional experimentation during their teens (no more than an estimated 20 lifetime episodes). None of the controls had ever tried cannabis-based medicines. Urine drug screening indicated that all non-users tested negative for cannabinoids and other non-medicinal substances.

3.3 PSYCHIATRIC ASSESSMENT AND FATIGUE

The lifetime prevalence of major depression for the entire sample was 56.0%. Lifetime prevalences for anxiety disorders were as follows: generalized anxiety disorder 26.0%; panic disorder 20.0%; phobia 4.0%; obsessive compulsive disorder 2.0%; and post-traumatic stress disorder 4.0%. Lifetime prevalence for any of the anxiety disorders was 36.0%.

Psychiatric comparison between cannabis users and non-users are presented in Table 2. There were no significant differences between groups in the lifetime prevalences of psychiatric disorders and use of anti-depressant medication. Similarly, scores on HADS Depression and Anxiety subscales and the MFIS showed no significant differences between cannabis users and non-users (Table 2).

Table 2. Comparison of MS cannabis users and non-users on psychiatric variables and fatigue.

Variable	Cannabis users	Non-users	t or x^2	*p*
SCID- I Major depression, lifetime: n (%)	15 (60.0)	13 (52.0)	$x^2 = 0.325$	0.569
SCID- I Anxiety disorder, lifetime: n (%)	10 (40.0)	8 (32.0)	$x^2 = 0.347$	0.556
Antidepressants: n (%) taking	10 (40.0)	12 (48.0)	$x^2 = 0.325$	0.569
HADS - Depression subscore: Mean (SD)	7.0 (4.4)	6.7 (4.9)	t = 0.182	0.856
HADS - Anxiety subscore: Mean (SD)	8.8 (4.7)	7.00 (5.7)	t = 1.225	0.227
Modified Fatigue Impact Scale: Mean (SD)	46.3 (16.2)	40.4 (24.2)	t = 1.022	0.322

SCID-I: Structured Clinical Interview for the DSM-IV Axis I Disorders; HADS: Hospital Anxiety and Depression Scale

3.4 NEUROPSYCHOLOGICAL ASSESSMENT

The results of the neuropsychological assessment are presented in two sections. The first contains the results of univariate analyses on each cognitive measure. Although the cannabis users and non-users were group-matched on demographic and disease-related variables, regression analyses were conducted with the aim of exploring the effect of cannabis use on each cognitive measure independent of age, sex, education, alcohol consumption, EDSS, depression, anxiety and fatigue. The second section presents these results along with the findings of correlation analyses between cannabis-related variables and global cognitive impairment.

All analyses were conducted with and without inclusion of the one subject who indicated only ingesting cannabis in food products. None of the findings were significantly altered as a result of this. Therefore only findings with the inclusion of this subject are presented.

3.4.1 Univariate Analysis

Neuropsychological comparisons between cannabis users and non-users along with effect sizes and post-hoc power analyses are presented in Table 3.

Learning and Memory

The California Verbal Learning Test (CVLT-II) was administered to assess verbal learning and memory. There were no significant differences between cannabis users and non-users on two primarily outcome measures, Immediate and Delayed Free Recall (Table 3). Post-hoc power analysis revealed ß of 0.709 and 0.754 for CVLT-II Immediate and Delayed Recall respectively (Table 3), suggesting a low probability of a Type II error. There was also no significant between-group differences on the List B Recall, where cannabis users recalled 4.7 ± 1.92 words compared to 5.6 ± 2.08 recalled by non-users (t = -1.486, p = 0.144). On the Short Delay trials, cannabis users and non-users performed similarly on the Free Recall (cannabis users: 10.0 ± 3.3, non-users: 10.6 ± 3.2; t = -0.743, p = 0.461) and Cued Recall trials (cannabis users: 11.2 ± 2.9, non-users: 12.2 ± 2.8; t = -1.273, p = 0.210). There were also no significant differences in the Delayed Cued Recall (cannabis users: 11.4 ± 3.5, non-users: 12.0 ± 2.5; t = -0.765, p = 0.448). There was no significant difference between groups in the number of intrusions across all trials (cannabis users: 5.6 ± 8.1, non-users: 3.4 ± 4.7; t = 1.181, p = 0.244), however cannabis users made significantly more perseveration errors across all trial (7.0 ± 4.0) compared to non-users

(4.4 ± 3.8; t = 2.387, p = 0.021). On the Recognition Trial, there were no significant differences between cannabis users and non-users on the number of Hits (cannabis users: 15.0 ± 1.1, non-users: 14.9 ± 1.5; t = 0.325, p = 0.747) and False Alarms (cannabis users: 3.0 ± 5.4, non-users: 1.7 ± 3.0; t = 0.998, p = 0.323).

The Brief Visuospatial Memory Test (BVMT-R) was administered to examine visuospatial learning and memory. There were no significant differences between cannabis users and non-users on Immediate or Delayed Recall with ß values of 0.863 and 0.790, respectively (Table 3), suggesting a low probability of a Type II error. On average, cannabis users had a Learning Score (improvement after Trial 1) of 3.5 ±2.26 compared to 4.32 ± 2.16 in non-users (t = -1.282, p = 0.206). On the Delay Recall Percent Retained, cannabis users and non-users retained 92.5 and 90.7 percent, respectively, of previously acquired information (t = 0.633, p = 0.637). On the BVMT-R Recognition Trial, cannabis users and non-users did not differ on the number of Hits (cannabis users: 5.52 ± 0.770; non-users: 5.40 ± 0.913; t = 0.502, p = 0.618) and False Alarms (cannabis users: 0.200 ± 0.577; non-users: 0.040 ± 0.200; t = 1.309, p = 0.197).

Verbal Fluency

The Controlled Oral Word Association Test (COWAT) is a measure of phonemic fluency. There was no significant difference between cannabis users and non-users on the total number of correct responses across the three trials (Table 3). The ß value of 0.733 suggests that it is unlikely that this finding was due to a Type II error. Cannabis users and non-users also did not differ on the number of preservations (t = 0.393, p = 0.696) or intrusions (t = 1.049, p = 0.299).

Visuospatial Perception

Judgment of Line Orientation (JLO) is a measure of visuospatial perception. The outcome measure was the total number of correct responses adjusted for age and sex. On this test, cannabis users had significantly lower scores than non-users, with a medium effect size of 0.68 (Table 3).

Executive Functioning

The D-KEFS Sorting Test taps into several executive functions including abstraction and conceptual thinking. On this test, cannabis users scored significantly lower than non-users on

both the number of correct sorts (Sorting Score) as well as the Description Score, with medium effect sizes of 0.74 and 0.60, respectively (Table 3).

Information Processing Speed

The Paced Auditory Serial Addition Test (PASAT), a measure of information processing speed and working memory, consists of two versions: 3-second (PASAT-3) and 2-second (PASAT-2) inter-stimulus intervals. Cannabis users had significantly lower scores on both PASAT-3 and PASAT-2 compared to non-users. Effect size was medium (0.68) for PASAT-2 and strong (0.90) for PASAT-3 (Table 3).

The Symbol Digit Modality Test (SDMT) also probes information processing speed as well as attention. Cannabis users had a significantly lower number of correct responses compared to non-users, with a medium effect size of 0.66 (Table 3).

Global Cognitive Impairment

Of all 50 patients, 24 (48.0%) were classified as cognitively impaired, scoring 1.5 SD or more below published norms on two or more of the cognitive measures. Cannabis users were twice as likely to be classified as cognitively impaired compared to non-users (16 cannabis users vs. 8 non-users globally cognitively impaired; $X^2 = 5.13$, $p = 0.024$; Table 3). The period of abstinence from cannabis use (12-24 hours vs. greater than 24 hours) was not associated with global cognitive impairment ($X^2 = 0.198$, $p = 0.673$).

Table 3. Univariate analyses comparing MS cannabis users and non-users on cognitive measures.

Cognitive Domain	Cognitive test	Cannabis users	Non-users	t or x^2	*p*	*Cohen's d*	*Power (one-tailed)*
Learning and Memory: Mean (SD)	CVLT-II Immediate Recall	49.5 (10.9)	52.5 (11.2)	t = -0.969	0.337	0.27	0.709
	CVLT-II Long Delay Recall	10.6 (3.6)	11.2 (2.7)	t = -0.681	0.499	0.19	0.754
	BVMT-R Total Recall	22.1 (8.3)	22.8 (7.6)	t = -0.284	0.777	0.09	0.865
	BVMT-R Delay Recall	8.2 (3.1)	8.7 (3.1)	t = 0.545	0.588	0.16	0.790
Verbal fluency: Mean (SD)	COWAT Total Score	31.0 (11.9)	33.7 (10.8)	t = -0.845	0.403	0.24	0.733
Visuospatial perception: Mean (SD)	JLO Score*	23.9 (4.7)	26.7 (3.5)	t = -2.417	0.020	0.68	0.615
Executive functioning: Mean (SD)	D-KEFS Sorting Score	8.4 (2.4)	10.3 (2.7)	t = -2.704	0.009	0.74	0.566
	D-KEFS Description Score	31.4 (9.5)	37.4 (10.4)	t = -2.127	0.039	0.60	0.626
Information processing speed: Mean (SD)	PASAT-3	36.0 (12.0)	44.0 (11.4)	t = -2.402	0.020	0.68	0.615
	PASAT-2	26.1 (7.6)	35.0 (11.7)	t = -3.188	0.003	0.90	0.620
	SDMT Total	42.4 (11.4)	50.4 (12.9)	t = -2.329	0.024	0.66	0.619
Global Cognitive Impairment: n (%) impaired	≤1.5 SD on 2 or more of 11 cognitive tests: n (%)	16 (64.0)	8 (32.0)	$x^2 = 5.128$	0.024	-	-

CVLT: California Verbal Learning Test; BVMT-R: Brief Visuospatial Memory Test-Revised; COWAT: Controlled Oral Word Association Test; JLO score: Judgment of Line Orientation; D-KEFS: Delis-Kaplan Executive Functions Test; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modality Test.

* JLO score corrected for sex and age.

3.4.2 Regression and Correlation Analyses

Multiple linear regressions were conducted using each cognitive measure as a dependent variable to examine the influence of Group (cannabis user vs. non-user) on cognitive performance independent of potential confounding factors (age, sex, education, EDSS, alcohol consumption, HADS Depression and Anxiety subscores, and MFIS). The final regression models are presented in Table 4 and reveal that cannabis use was a significant independent predictor of performance on the JLO, D-KEFS Sorting Score, PASAT-2, and SDMT, but not on the CVLT-Immediate Recall, CVLT-Delayed Recall, BVMT-Immediate Recall, BVMT-Delayed Recall, COWAT, PASAT-3 and D-KEFS Description Score (Table 4).

Binary logistic regression analysis was conducted with global cognitive impairment as the dependent variable and Group (cannabis user vs. non-user) and the potential covariates as independent variables. The final model, also presented in Table 4, showed that group remained a significant independent predictor of global cognitive impairment.

Global cognitive impairment was not significantly correlated with urine cannabinoid levels (r= -0.321, p = 0.118), age of cannabis use onset (r = -0.321, p = 0.118) or duration of cannabis use (r= 0.158, p = 0.451), although the trends were in the hypothesized directions.

Table 4. Regression analyses comparing MS cannabis users and non-users on cognitive measures.*

Cognitive Domain	Cognitive test indices	Covariates†	B (95% CI)	*p*
Learning and Memory	CVLT-II Immediate Recall	Sex Education EDSS Alcohol consumption HADS Anxiety	1.451 (-5.093, 7.995)	0.657
	CVLT-II Long Delay Recall	Sex Education EDSS Alcohol consumption HADS Anxiety MFIS	0.399 (-1.286, 2.084)	0.635
	BVMT-R Total Recall	Sex Education EDSS Alcohol consumption HADS Anxiety MFIS	-0.315 (-5.156, 4.526)	0.896
	BVMT-R Delay Recall	Education EDSS Alcohol consumption HADS Anxiety MFIS	0.215 (-1.806, 2.235)	0.831
Verbal fluency	COWAT Total Score	Sex Education EDSS HADS Anxiety MFIS	1.832 (-5.115, 8.779)	0.533
Visuospatial perception	JLO Score	HADS Anxiety MFIS	2.904 (0.545, 5.263)	0.017
Executive functioning	D-KEFS Sorting Score	Education Alcohol consumption	1.676 (0.274, 3.077)	0.020
	D-KEFS Description Score	Education EDSS Alcohol consumption	4.943 (-0.663, 10.548)	0.083
Information processing speed	PASAT-3	Sex Education Alcohol consumption HADS Anxiety	4.355 (-2.600, 11.310)	0.214
	PASAT-2	Education	8.007 (2.347, 3.667)	0.007
	SDMT Total	EDSS Alcohol consumption	7.116 (0.337, 13.895)	0.040
Global Cognitive Impairment	≤1.5 SD on 2 or more of 11 cognitive tests: n (%)	Education	-1.468 (1.265, 14.887)	0.020

*All models contained Group as a predictor. Model parameters are presented for cannabis group after controlling for confounds.

†Only variables that changed the coefficient for cannabis group by 10 percent or more were retained in the final model as covariates.

CVLT: California Verbal Learning Test; BVMT-R: Brief Visuospatial Memory Test-Revised; COWAT: Controlled Oral Word Association Test; JLO score: Judgment of Line Orientation; D-KEFS: Delis-Kaplan Executive Functions Test; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modality Test. MFIS: Modified Fatigue Impact Scale; EDSS: Expanded Disability Status Scale; HADS: Hospital Anxiety and Depression Scale.

CHAPTER 4: DISCUSSION

This is the first prospective cross-sectional study examining the cognitive effects of smoked or ingested cannabis use in MS patients. Two groups of MS patients, cannabis users and non-users, were compared on measures of verbal and visuospatial learning and memory, verbal fluency, visuospatial perception, executive functioning and information processing speed. The groups were equated with respect to demographic and disease-related variables that could potentially influence cognitive performance. In addition, subsequent regression analysis was conducted using age, sex, education, alcohol consumption, level of disability, depression, anxiety and fatigue as covariates to statistically control for the effects of these extraneous variables.

Cannabis users had greater deficits on information processing speed, executive functioning, and visuospatial perception compared to a sample of non-users group-matched on age, sex, education, premorbid intelligence, EDSS, as well as disease course and duration. Cannabis users were also twice as likely as non-users to meet the criteria for global cognitive impairment. All but two of these between-group differences (PASAT-3 and D-KEFS Description score) were retained after controlling for potential confounds in the regression analysis.

In contrast to findings from the general population which have consistently noted deficits in learning and memory in chronic cannabis users (Block & Ghoneim, 1993; Fried et al., 2005; Solowij et al., 2002; Pope et al., 2001), the findings of the present study indicate that cannabis use is not associated with further decrements in verbal and visuospatial learning and memory in patients with MS. Cannabis users performed similarly to non-users on CVLT-II Immediate and Delayed Recall. There was no significant group difference on List B Recall or Short Delay Free Recall, suggesting that cannabis does not affect proactive (List B Recall) and retroactive (Short Delay Free Recall) interference. Both groups also performed similarly on the Recognition Trial, on average recalling 15 out of 16 target words correctly. This is consistent with studies showing relatively preserved recognition memory in MS patients (Rao, 1989a). There was also no difference between cannabis users and non-users on the number of intrusions made, although cannabis users made significantly more perseveration errors across all acquisition trials. Perseveration errors are believed to reflect memory dysfunction and impaired attention (Hotz & Helm-Estabrooks, 1995) and previous studies have found that patients with MS produce greater

perseverations on tests of verbal free recall (Griffiths et al., 2005). The present findings suggest that cannabis use can further contribute to this deficit.

There were also no between-group differences on the BVMT-R Immediate and Delayed Recall. Both groups had high scores on the Delay Recall Percent Retained, which is the proportion of visuospatial information retrieved relative to that initially acquired. This finding supports the view that impaired recall on memory tests is related to deficits in the initial acquisition of information rather than retention or retrieval. Cannabis users and non-users performed similarly on the BVMT-R Recognition Trial, correctly identifying nearly all target items with few False Alarms.

The effect of cannabis use on verbal fluency is unclear since the only study reporting deficits in this domain in heavy cannabis users failed to account for the lower verbal IQ in their sample (Pope & Yurgelun-Todd, 1996). In the present study, no significant differences were found between cannabis users and non-users on the COWAT (total number of words, and number of perseverations and intrusions), suggesting that cannabis use is not associated with further decrements in word retrieval and verbal fluency in patients with MS.

In the general population literature, decreased perceptual accuracy (Soueif, 1976a) and longer reaction times on a test of visual scanning (Ehrenreich et al., 1999) have been found in cannabis users. However, performance on untimed tests of visuospatial perception has not been investigated in cannabis users. In this study, cannabis users had reduced accuracy on the JLO, suggesting that cannabis exacerbates deficits in patients with MS who are already vulnerable to poorer performance in this domain.

Cannabis use in the general population has been associated with deficits on executive functioning (Medina et al., 2007; Pope & Yurgelun-Todd, 1996). Patients with MS are also prone to such deficits (Parmenter et al., 2007a; Benedict et al., 2006; Drew et al., 2008; Rao et al., 1991a). Therefore, it is not surprising that the present study found that patients with MS who use cannabis performed significantly more poorly than non-users on the D-KEFS Sorting Test. Whereas univariate analysis revealed that both the Sorting and Description scores were significantly lower among cannabis users, in the final regression model the D-KEFS Description Score failed to reach statistical significance (Table 4). Three covariates were retained in the

model, namely education, EDSS and alcohol consumption. It is therefore plausible that these variables, particularly alcohol consumption which was non-significantly greater in cannabis users, may mediate some of the deficits on executive functioning found in cannabis users.

Reports of poorer performance on measures of information processing speed and attention among cannabis users are widespread (Hanson et al., 2010; Solowij et al., 2002; Croft et al., 2001; Ehrenreich al., 1999; Pope & Yurgelun-Todd, 1996; Fletcher et al., 1996; Medina et al., 2007; Wadsworth et al., 2006; Fried et al., 2005). Similarly, patients with MS are prone to significant declines in these domains (Beatty et al., 1989; Rao et al., 1991a). Expectedly, patients with MS who use cannabis performed significantly poorer than non-users on all three measures of information processing speed and attention (PASAT-3, PASAT-2, and SDMT). After controlling for potential covariates, cannabis use failed to predict PASAT-3 performance but remained a significant predictor of PASAT-2 and SDMT performance. Given that the PASAT-2 is merely a more cognitively challenging version of PASAT-3, this latter finding raises the possibility that cannabis use by patients with MS is more likely to have an adverse effect on tasks requiring greater cognitive effort and that less cognitively challenging tasks are not as likely to be affected.

Cognitive dysfunction affects approximately 40-65% of MS patients (Rao et al., 1991a; Lyon-Caen et al., 1986) with detrimental effects on personal, social and occupational functioning (Rao et al., 1991b) as well as quality of life (Benito-Leon, Morales, & Rivera-Navarro, 2002). In this study, 48.0% of the entire sample was classified as globally cognitively impaired. Cannabis users were twice as likely as non-users to have cognitive impairment, pointing to adverse effects of cannabis on this cognitively vulnerable group. Although not the focus of the present investigation, it is plausible that the additional cognitive deficits associated with chronic cannabis use may have deleterious psychosocial ramifications. For example, in this study cannabis users were twice as likely as non-users to be unemployed. This is unlikely to be related to differences in level of disability given that the groups had comparable EDSS scores. While the reasons for the higher unemployment rate among cannabis users in this study are not clear, an association between impaired cognitive performance and unemployment in patients with MS has been reported (Beatty, Blanco, Wilbanks & Paul, 1995; Honarmand et al., 2010), thereby suggesting a putative link with the present findings.

To date, the clinical trials literature on the effects of cannabis on cognition in MS patients is sparse, largely limited to synthetic cannabis derivatives or cannabis-based extracts, with measures of cognition usually confined to secondary analysis. Results are equivocal with deficits in long-term memory storage reported by one study (Rog et al., 2005) contrasting with an absence of deleterious cognitive problems associated with cannabinoids reported by others (Vaney et al., 2004; Wade et al., 2004; Aragona et al., 2009). The duration of cannabinoid administration in these studies ranged from 2 to 14 weeks. The short duration of cannabinoid exposure as well as differences in the pharmacokinetic profile of oral and inhaled cannabinoids may account for the sparse reports of deleterious cognitive effects.

The results of this investigation are consistent with data from an earlier pilot study which revealed that MS patients who smoked cannabis performed significantly more poorly than cannabis naïve patients on a test of information processing speed (Ghaffar and Feinstein, 2008). By virtue of a more robust methodology, this study confirms and extends these earlier results and links smoked or ingested cannabis to more extensive cognitive deficits.

The paucity of cognitive data pertaining to the use of inhaled cannabis in patients with MS contrasts with a much larger literature obtained from general population studies. Results here have varied according to the timing of the neuropsychological inquiry. In the present study, the time frame for neuropsychological testing was set at greater than 12 hours following the last inhalation or ingestion of cannabis. The literature from the general population suggests, with few exceptions (Carlin & Trupin, 1977), that there are residual, adverse cognitive effects during this period (Pope et al., 2001; Fried et al., 2005; Solowij et al., 1995b). Our findings replicate this picture in patients with MS and points towards the detrimental effects of cannabis persisting beyond the period of intoxication.

The present data diverged from the general population finding of higher rates of psychopathology, mainly depression and anxiety disorders in cannabis users (Cheung et al., 2010). This pertained both to the lifetime prevalence of these disorders and current indices of emotional distress as captured by the HADS. This result may, in part, be attributed to the already high prevalence of depressive and anxiety disorders associated with MS itself (Minden & Schiffer, 1990; Korostil & Feinstein, 2007). The lifetime prevalence of major depression and

anxiety disorders were similarly high in this study, with over half of subjects having had major depression and 36% one or more anxiety disorders over their lifetime.

Cognitive dysfunction was not associated with the level of cannabinoid metabolites detected in the urine, the age of onset, or the duration of cannabis use. It is possible that the lack of association may be an artifact of the sample selection where the overwhelming majority of cannabis users began using the drug in adolescence and in whom urinary levels of metabolites clustered tightly at the upper limits of the range of detection.

The demographic and disease-related characteristics of this sample, including age, years of education, disease course and duration, and EDSS, were for the most part similar to those of other studies. In contrast to other studies where the ratio of females to males is approximately three to one, the ratio in this sample was less than one. A greater proportion of male patients were recruited in the cannabis group, consistent with previous reports that male patients are more likely to use cannabis (Clark et al., 2004; Chong et al., 2006). Therefore, the non-user control sample was selected with a similar proportion of males and females in order to ensure that the groups were matched on this potential confounding variable.

Previous studies have found that cannabis users have lower scores on measures of premorbid intelligence (Fried et al., 2005; Lyons et al., 2004). In an attempt to avoid the potential confound of premorbid intelligence, cannabis users and non-users were group-matched on the ANART verbal IQ scores in addition to level of education. The latter variable was also included as a covariate in the regression analyses. Therefore, it is unlikely that differences in premorbid intelligence can account for the poorer cognitive performance in cannabis users.

While the present study did not address the etiology behind the residual effects of cannabis on cognition, several conjectures can be posed. Withdrawal effects resulting from a short period of cannabis abstinence may account for the residual cognitive deficits, particularly in heavy users. However, given that withdrawal symptoms typically emerge within 1-2 days and peak between 2 to 6 days after abstinence (Budney et al., 2004), this explanation does not account for the deficits observed prior to and beyond this time frame nor the presence of cognitive deficits in light cannabis users. Furthermore, this study found no difference in global cognitive impairment between those who had abstained for 12 to 24 hours in whom withdrawal effects are not

expected compared to those who had abstained for over 24 hours in whom withdrawal effects are more likely. Nonetheless, the role of withdrawal effects following a brief period of abstinence on the short-term residual effects of cannabis remains to be elucidated.

Another explanation is that cannabinoid residues that linger in the body for several weeks following the last consumption continue to exert deleterious effects on the CNS, adversely affecting cognition. Chronic cannabis use leads to the accumulation of cannabinoid metabolites in the body, some of which are stored in fat cells and released intermittently following cessation of cannabis use (Pope et al., 2001). Given that the clearance of cannabinoid metabolites from the body is relatively slow (Ashton, 2001), it is plausible that any deficits after a short period of abstinence may be due to the presence of these residues in the CNS.

Functional neuroimaging data from MS patients have consistently shown that in response to a cognitive challenge, ancillary brain activation occurs as a compensatory response to the presence of cerebral pathology (Sweet et al., 2006; Forn et al., 2007). Altered or more widespread patterns of brain activation have also been reported in cannabis users without MS (Kanayama et al., 2004; Eldreth et al., 2004; Gruber & Yurgelun-Todd, 2005; Block et al., 2002; Chang et al., 2006). It is therefore plausible that the deleterious effects of cannabis in patients with MS may be associated with overwhelmed compensatory responses as a result of MS-related cerebral injury compounded by the effects of chronic cannabis use and the cognitive challenge. In addition, functional neuroimaging findings have demonstrated lower *resting* global and prefrontal blood flow in cannabis users even before they are challenged with a cognitive task (Martin-Santos et al., 2010). These resting state data suggest a degree of "background" cerebral compromise may further complicate cognitive functioning. Further research is needed to replicate these findings in a larger sample and to explore the cerebral underpinnings of how these changes may come about.

The results of the present investigation are derived from patients who have used cannabis on a regular basis, as much as several times per day for more than two decades, and therefore do not necessarily extend to occasional cannabis use or frequent use for a brief period of time. Indeed, studies of cannabis use in healthy individuals have shown that the cognitive effects of cannabis are dose-dependent, with deficits primarily observed in heavy cannabis users (Fried et al., 2005; Solowij et al., 1995b) and those who use cannabis over a long period of time (Solowij et al. ,

1995b). As previously discussed, there is some evidence from the general population literature to suggest a gradual improvement in cognitive functioning following a longer period of abstinence (Pope et al., 2001). While the reversibility of the cognitive deficits in patients with MS following long-term abstinence from the drug is plausible, this possibility was not addressed by the present investigation. This study also did not address the mechanisms leading to the residual effects of cannabis on cognition. While it is likely that these persistent deficits are due to the residual effects of the drug itself on the CNS compounding MS-related cerebral pathology, whether and to what extent withdrawal effects contribute as well cannot be ascertained from our data. Furthermore, the effect of tobacco smoking status and the potential contribution of recent tobacco use or withdrawal were not explored. Another limitation of this study is the cross-sectional design, which limits the ability to establish a cause and effect relationship between cannabis use and greater cognitive dysfunction. Finally, the modest sample size introduces a further cautionary note.

Future Directions

The results of the present study, should they be replicated in larger samples, raise several avenues for future research. As previously discussed, these findings are based on a sample of heavy, long-term cannabis users. Therefore, the effects of occasional or brief cannabis use must be explored in patients with MS. In addition, the present results are applicable to the short-term residual effects of cannabis on cognition in patients with MS following a brief period of abstinence. Further research is required to delineate the acute effects as well as any long-term residual (chronic) effects of cannabis use in this population. While it is plausible that long-term abstinence from the drug may lead to the recovery of some or all of the cognitive deficits observed in this study, it is also possible that deficits would persist even after the drug has been cleared from the body. Longitudinal studies of patients with MS who abstain from cannabis for longer periods of time are required to determine whether and to what extent recovery of function occurs over time.

Also unclear from the present investigation, is the role of cerebral function in cognitive dysfunction associated with cannabis use in patients with MS. It is plausible that MS-related cerebral injury is compounded by the effects of chronic cannabis use, overwhelming neural compensatory mechanisms. To address these possibilities, neuroimaging studies are required to

examine the patterns of neural activation in response to varying degrees of cognitive challenge in MS patients who use cannabis.

Conclusions

The present study found that MS patients who use cannabis had greater deficits on measures of information processing speed, executive functioning, and visuospatial perception compared to non-users. Cannabis users were also twice as likely as non-users to meet the criteria for global cognitive impairment. The deficits were apparent beyond the period of acute intoxication. These findings raise concerns about the utility of this drug in the management of MS-related symptoms over an extended period of time. Of further concern is the paucity in studies investigating the persistence of these cognitive deficits in patients with MS following a longer period of abstinence. In light of the high prevalence and adverse consequences of cognitive dysfunction in patients with MS, it is plausible that the further cognitive burden introduced by chronic cannabis use may interfere with social, personal and occupational functioning of patients. Given the high prevalence of cannabis use in this population, further research is needed to replicate these findings and to explore the cerebral underpinnings of cognitive dysfunction associated with cannabis use in patients with MS.

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Appendices

APPENDIX A: Pre-screening Questionnaire

First Name: _____ Last Name: _____

Gender: Male ☐ Female ☐

Age: _____

Are you currently involved in other research studies? Yes ☐ No ☐

Have you ever had a head injury in which you lost consciousness? Yes ☐ No ☐

Other illnesses (e.g., vascular problems, other neurological conditions): _____

Do you currently or have you in the past 3 months used illicit drugs: Yes ☐ No ☐

☐ Opiates (Morphine, codeine, heroin)
☐ PCP
☐ LSD
☐ Stimulants
☐ THC (Marijuana)
☐ Amphetamines (Methamphetamine, MDA/MDMA)
☐ Benzodiazepines
☐ Barbiturates

Cannabis use:

Notes:

APPENDIX B: DEMOGRAPHIC SURVEY

Gender: Male ☐ Female ☐ Age: _____

Marital Status: Single ☐ Married ☐ Widowed ☐ Divorced ☐ Common-law ☐

Highest level of education obtained: High School ☐
College ☐
Bachelors ☐
Post-Graduate ☐

Employed: Yes ☐ No ☐ Occupation: _____

Medications: None ☐
Copaxone ☐
Rebif ☐ (Dosage? Low ☐ High ☐)
Betaseron ☐ (Dosage? Low ☐ High ☐)
Avonex ☐
Other _____

Steroids in Past 3 months? Yes ☐ No ☐

Disease Course: Relapsing/Remitting ☐
Secondary Progressive ☐
Progressive Relapsing ☐
Primary Progressive ☐

Disease Duration in Months: _____ Duration since Diagnosis (Months): _____ EDSS: _____

Exacerbations: Yes ☐ No ☐ Severity of Exacerbations (explain): _____

History of MS in Family: Yes ☐ No ☐

History of Psychiatric illness: Yes ☐ No ☐
Depression ☐
Bipolar ☐
Substance abuse ☐
Anxiety disorder ☐
Schizophrenia ☐
Other _____

Past Psychiatric Admission: Yes ☐ No ☐

Other illnesses: _____

Alcoholic Drinks/week: _____ Males > 14
Females > 9

Use of street-purchased cannabis: Yes ☐ No ☐ Use of medicinal cannabis: Yes ☐ _____ No ☐

	First use?	Frequency of use	Amount of use on each occasion	Type of cannabis used	Last time used?	Medicinal, recreational or both?
THC (Marijuana)						

APPENDIX C: INFORMED CONSENT FORM

Consent to Participate in a Research Study

Title of Research Study: Cannabis use in multiple sclerosis: A cognitive and neuroimaging study

Investigators:
Dr. Anthony Feinstein, MD, PhD Sunnybrook Health Sciences Centre 416-480-4216
Dr. P. O'Connor, MD, MSc, FRCPC St. Michael's Hospital 416-864-5830
Assistant: Kimia Honarmand Sunnybrook Health Sciences Centre 416-480-6100x7626
Sponsor: Multiple Sclerosis Society of Canada

You are being asked to consider participating in a research study. This form explains the purpose of this research study, provides information about the study, the tests and procedures involved, possible risks and benefits, and the rights of participants.

It is important that you read the information in this form carefully and ask any questions you may have before agreeing to take part in this research study. You may take as much time as you wish to decide whether or not to participate. Please ask the study staff or the study doctor to clarify anything you do not understand or would like to know more about. All research is voluntary. You may also wish to discuss the study with your family doctor, a family member or close friend. If you decide to take part in the study, it is important that you are completely truthful about your health history and any medications you are taking. This will help prevent any unnecessary harm to you.

Purpose of this Research Study

You are being asked to consider participating in this study because you have multiple sclerosis (MS). The purpose of this study is to examine whether cannabis use has any positive or negative effects on cognition and whether these are related to differences in the brain. This study looks at the cognitive performance of individuals with MS and examines the relationship between performance and brain structure. The findings of this study can have important effects on determining cognitive abilities of individuals with MS.

How many people will take part in the study?

It is anticipated that about 90 people will participate in this study at Sunnybrook Health Sciences Centre and St. Michael's Hospital. The entire study is expected to take about 2 years to complete.

Description of the Research

All testing will occur during 1 visit to Sunnybrook Health Sciences Centre. For this study, you will be required to complete one general questionnaire regarding you're your educational background, occupation and other demographic information. You will then complete a brief vision test, motor coordination test and walking test. You will then be asked a series of questions regarding your overall mood, your history of depression and anxiety and any past or present drug use. Then you will be asked to perform a series of several brief cognitive tests, which are part of the standard group of tests used to test memory in individuals with MS. These tests will assess cognitive functions such as memory, visual spatial learning, attention, and speed of information processing. Then, you will undergo magnetic resonance imaging (MRI) brain scanning, which will require you to lie down inside the scanner for approximately one hour. Finally, you will be asked to provide a urine sample that will be analyzed for levels of various drugs. Testing will take approximately 4 hours in one session, including 20 minute break.

What are the responsibilities of study participants?

If you decide to participate in this study you will be asked to do the following:

- Visit Sunnybrook Health Sciences Centre to participate in one 4-hour study.
- You will also be asked to provide a urine sample, which will be stored in our facilities at Sunnybrook Health Sciences Centre and later transported to the Hospital for Sick Children where drug testing will be done to determine the presence of the following drugs in urine: narcotics (e.g., morphine, codeine), barbiturate, sedatives, stimulants (e.g., methamphetamine, cocaine), and levels of cannabis.

The results of the urine test will be anonymous, and will not be associated with your identifiable information.

- You will be asked to complete questionnaires, answer questions regarding your overall mood, and perform several cognitive tests as described above.
- You will undergo MRI brain scanning.

MRI Scan

You will have an MRI brain scan during this research study. An MRI is a scanning technique that uses magnetic fields to provide a picture of the structure of the brain. To do the MRI scan you will be placed on a scanning table, such that your head will be within the camera-ring, without skin contact. The scanning takes approximately one hour.

Potential Risks of MRI scan

There are no known special health risks associated with the MRI brain scan. The procedure does not involve exposure to radiation. 10% of subjects may experience MRI claustrophobia. Because MRI utilizes strong magnetic fields, the MRI scan should be avoided with subjects who have metallic foreign bodies or pacemakers, and you must make sure that you do not carry those items in your head or body.

What are the risks or harms of participating in this study?

There are no known risks from completing the questionnaire or the cognitive tests. You may or may not feel challenged or discouraged by the difficulty of the cognitive tests that you will be asked to complete. Should you may feel bored, fatigued or uncomfortable throughout testing, you may take a break and continue the experiment when you are ready.

What are the benefits to participating in this study?

You may or may not benefit directly from participating in this study. However, possible benefits include the option to receive feedback on your cognitive performance from a neuropsychiatrist at a later date. This information will be provided to you following the study. You may also receive a copy of your brain scan images on a disk to present to your neurologist for assessment. Your participation may or may not help other people with multiple sclerosis in the future.

What are the costs of participating in this study?

Participating in this study may result in added costs to you for transportation and lunch. You will receive a parking voucher to cover any parking costs or $10 to cover transportation costs when you visit Sunnybrook Health Sciences Centre to take part in the study.

Participation and Withdrawal

Your participation in research is voluntary. If you choose not to participate, you will continue to have access to customary care at Sunnybrook Health Sciences Centre. If you choose to participate in the study, you can withdraw from the study at any time without any affect on the care you will receive at Sunnybrook Health Sciences Centre. Withdrawal from the study does not necessarily include withdrawal of any data compiled up to that point. Should you choose to end the study early, please inform the research assistant.

The study doctors may decide to remove you from this study without your consent for any of the following reasons:

- The study doctors decide that continuing in this study would be harmful to you.
- You are unable or unwilling to follow the study procedures.

If you are removed from this study, the investigators will discuss the reasons with you.

Confidentiality and Privacy

The results of this study are confidential. If you choose to participate in the study, you will be assigned a random code which will be used to input all the information and results collected in the study. Your name will not be associated with your responses to questionnaires, your performance on cognitive tests, the results of the urine test or the MRI data. Your confidentiality will be respected and no information that discloses your identity will be released or published without consent unless required by law.

Publication of Results

Results from this study may be published, presented at conferences, seminars or other public forums. Confidentiality of subjects will be maintained. Neither your identity nor any personal information will be available to anyone other than the investigators. No personal information will be disclosed in any

resulting publication or presentation. The sponsor may dispose of the results of this study and may choose not to publish or make use of the results of the study.

Contact

If you have any questions as a research subject you may contact Dr. Philip Hébert, Chair of the Sunnybrook Research Ethics Board at 416-480-4276 or the study doctors (their contact information is at the top of this form).

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish translated into your preferred language.

2. Participating in this study is your choice (voluntary). You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, it will not have any effect on your future medical treatment or health care.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study.

4. By signing this consent form, you do not give up any of your legal rights.

5. You have the right to receive a copy of this signed and dated informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. If you become sick or injured as a direct result of your participation in this study, your medical care will be provided.

8. Any of your personal information (information about you and your health that identifies you as an individual) collected or obtained, whether you choose to participate or not, will be kept confidential and protected to the fullest extent of the law. All personal information collected will be kept in a secure location. The study staff will have access to your personal information for purposes associated with the study, but will only be allowed to access your records under the supervision of the Principal Investigator and will be obligated to protect your privacy and not disclose your personal information. None of your personal information will be given to anyone without your permission unless required by law. When the results of this study are published, your identity will not be disclosed. The data for this study will be retained for 5 years.

9. If, as a result of your participation in this study, any new clinically important medical information about your health is obtained, you will be given the opportunity to decide whether you wish to be made aware of that information.

10. You have the right to access, review and request changes to your personal information (i.e. address, date of birth).

11. You have the right to be informed of the results of this study once the entire study is complete.

DOCUMENTATION OF INFORMED CONSENT

Full Study Title: Cannabis use in multiple sclerosis: A cognitive and neuroimaging study

Name of Participant: _____

Participant

By signing this form, I confirm that:

- This research study has been fully explained to me and all of my questions answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study and my right not to participate as well as the right to withdraw without compromising the quality of care I receive at this or any other health care institution
- I have been informed of the rights of research participants
- I have read each page of this form
- I authorize access to my personal health information (medical record) and research study data as explained in this form
- I have agreed to participate in this study to participate in this study
- I understand that I have not waived my legal rights nor released the study doctors, sponsors, or involved institutions from their legal and professional duties.
- This informed consent document will be placed in my medical records

_____	_____	_____
Name of participant (Print)	Signature	Date

Person obtaining consent

By signing this form, I confirm that:

- I have explained this study and its purpose to the participant named above
- I have answered all questions asked by the participant
- I will give a copy of this signed and dated document to the participant

_____	_____	_____
Name of Person obtaining consent (print)	Signature	Date

Statement of Investigator

I acknowledge my responsibility for the care and well being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research. I have delegated the explanation of this study to this subject to Kimia Honarmand.

_____	_____	_____
Name of Investigator	Signature	Date