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Decision making under risk in multiple sclerosis

by

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Abstract

Cognitive deficits affect approximately 50% of multiple sclerosis (MS) patients and are associated with disease-related neurodegeneration. Prior MS-studies found decision making impairments uncorrelated with patients' cognitive functions. Brain correlates of decision making in MS have not been established. The Game of Dice Task (GDT) measures decision making under risk and was used here for the first time in MS patients. I tested healthy controls with either cognitive or brain measures (each n=20), 13 mildly-disabled relapsing-remitting (RR) ("RR-1"), 9 RRMS moderately-disabled ("RR-2"), and 10 secondary progressive ("SP") MS patients. GDT was impaired in RR-2 and SP subgroups. GDT correlated with processing speed in all patients, but also with executive functions in RR-2 patients. Ventricular width measures indicated atrophy in RR-2 and SP. In all patients, atrophy correlated with decision making and processing speed. Decision making under risk is impaired in later-stage MS and is related to cognition and brain atrophy.

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List of Abbreviations

AMG: amygdala

BBB: blood-brain-barrier

BRB-N: The Brief Repeatable Battery of Neuropsychological Tests

BVMT-R: Brief Visual Memory Test-Revised

CGT: Cambridge Gambling Task

CIS: clinically isolated syndrome

CNS: central nervous system

COWAT: Controlled Oral Word Test

CSF: cerebrospinal fluid

CVLT-II: California Verbal Learning Test-II

D-KEFS: Delis-Kaplan Executive Function System

DLPFC: dorsolateral prefrontal cortex

EBV: Epstein-Barr virus

EDSS: Expanded Disability Status Scale

FHW: frontal horn width

fMRI: functional MRI

GDT: Game of Dice Task

GLM: general linear model

GM: gray matter

HC: healthy controls

ICD: intercaudate distance

ICR: intercaudate ratio

IGT: Iowa Gambling Task

IQ: intelligence quotient

JOLO: Judgment of Line Orientation

MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis

MRI: magnetic resonance imaging

MS: multiple sclerosis

MSFC: Multiple Sclerosis Functional Composite Score

NAWM: normal-appearing white matter

OFC: orbitofrontal cortex

PASAT: Paced Auditory Serial Addition Test

PD: Parkinson’s disease

PPMS: primary progressive multiple sclerosis

PRMS: primary relapsing multiple sclerosis

RR: relapsing-remitting

RRMS: relapsing-remitting multiple sclerosis

SDMT: Symbol Digit Modalities Test

SP: secondary progressive

SPMS: secondary progressive multiple sclerosis

SRT: Selective Reminding Test

TVW: third ventricle width

VMPFC: ventromedial prefrontal cortex

WLG: Word List Generation test

WM: white matter

WOF: Wheel of Fortune Task

I. INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder with an unpredictable course and widespread effects on the central nervous system. Approximately half of all MS patients develop a range of deficits in neurocognitive functions (Arnett & Strober, 2011). Decision making is a very important and frequently utilized neurocognitive function. Relatively little is known about the types and extent of decision making impairments in MS, especially compared to more commonly observed and assessed functions like attention, executive functions or memory. Virtually nothing is known about brain correlates of decision making in MS. Decision making can be understood as a complex neurocognitive function that encompasses both emotional and cognitive aspects. Either aspect contributes to a different degree depending on the specific decision making test.

The current thesis uses the Game of Dice Task (Brand et al., 2002); a decision making test that emphasizes cognitive aspects of decision making and has never been studied in MS. The work here attempts to provide further knowledge about the cognitive and neurodegenerative correlates of decision making in patients with MS. Ultimately, understanding the nature and determinants of decision making impairments in MS may lead to treatments that can improve the safety, independence and quality of life for patients. I start the following introduction with an overview on MS.

II. LITERATURE REVIEW

1. Multiple Sclerosis

Multiple sclerosis (MS) is a neurological, inflammatory, immune-mediated and neurodegenerative disease. Characteristic of the disease is the process of demyelination, the breakdown of fatty nerve myelin sheaths surrounding the axons of the brain and spinal cord, along with the formation of lesions, better known as lesions or plaques, particularly in the white matter (WM). This detrimental process of demyelination results in a reduction of neural signal conduction throughout the central nervous system (CNS) and manifests itself in a broad spectrum of signs and symptoms. Although MS is historically thought of as a WM disease, plaques are also found in the cortical gray matter (GM), leading to both WM and GM damage and atrophy, together that promote the progression of MS-related disability.

MS has an unpredictable course both amongst and across patients in that the experienced symptoms can vary as a function of the location and severity of each individual neurological lesion. An exacerbation of MS (also known as a relapse, attack, episode or flare-up) is associated with increased lesion activity. These attacks, or episodes, can involve the advent of new symptoms or the worsening of old symptoms. An episode can last for days, weeks, or months, and it often alternates with periods of few to no symptoms (remissions). Initial symptoms of MS commonly involve changes in visual acuity, diplopia (double vision), hearing loss, numbness, tingling or weakness in the limbs or face, vertigo, dysarthria (difficulty articulating words), ataxia, sexual dysfunction, and urinary frequency or urgency. Other symptoms, not physical in nature, include mood and/or personality changes, fatigue and cognitive difficulties. Prominent cortical signs, such as aphasia, apraxia, seizures, visual field loss, dementia and extrapyramidal symptoms, are extremely rare and considered unusual in MS (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000).

1.1. Epidemiology

MS is one of the most common neurological disorders to disable young and middle-aged adults. According to Rosati (2001), about 2.5 million people suffer from MS globally, with a world-wide disease prevalence rate between 2 and 150 per 100,000. The geographical prevalence of MS varies, but generally, MS is more prevalent with increasing geographical distance from the equator (Handel, Handunnetthi, Giovannoni, Ebers, & Ramagopalan, 2010; Skegg, Corwin, Craven, Malloch, & Pollock, 1987). This particular distribution pattern likely represents a combination of environmental factors, genetic differences, and discrepancies in surveillance for the disease. In Canada, a recent review across 9 epidemiological studies (Poppe, Wolfson, & Zhu, 2008) describes prevalence rates between 55.2 (found in Newfoundland and Labrador) and 350 cases (in other Atlantic provinces) per 100,000 people, with a cross-national prevalence of 240 per 100,000. These numbers confirm Canada as a country of very high MS prevalence. It should be noted that determining precise prevalence statistics is challenging because there are estimates that up to 20% of cases of MS go undetected in life, with only some appearing as a chance finding post-mortem (i.e., lesions commonly located in a periventricular distribution in the temporal, occipital and frontal lobes) (Gilbert & Sadler, 1983). These undetected cases also reveal that there is likely an underestimation of true prevalence and new incidence rates of this disease.

As in other autoimmune disorders, there are gender differences in prevalence of MS, with MS affecting approximately twice as many women than men. A systematic review of 28 epidemiologic studies found that, from 1955 to 2000, the estimated female to male ratio of MS incidence increased from 1.4 to 2.3 (Alonso & Hernan, 2008), and newer evidence suggests that the incidence of MS is still increasing in females (Koch-Henriksen & Sorensen, 2010). Although MS can occur at any age, the onset of MS is usually in early adulthood, with symptoms manifesting between 15-50 years of age. The median and mean ages of the onset of MS are 23.5 and 30 years of age, respectively (Confavreux &

Vukusic, 2006). The peak age of MS onset is about five years earlier for women than for men.

1.2. Etiology

The etiology of MS is still unknown, but is likely a combination of both genetic and environmental causes. Evidence for genetic influences comes from the 5% dizygotic and approximately 25-40% monozygotic concordance rates for twins (Handel, Handunnetthi, et al., 2010; Handunnetthi, Handel, & Ramagopalan, 2010). There are also differences in prevalence rates across different ethnic groups. Caucasians, especially those originally from Northern Europe/Nordic regions (who typically live in temperate zones and in high-income countries), appear to have the highest risk for developing MS; while people of Asian, African, or American Indian origin (who often live in lower-income countries and in tropical zones) have the lowest risk (Koch-Henriksen & Sorensen, 2010). Ethnic evidence such as this is also supported by geographical observations that MS is more commonly found at latitudes further from the equator in both directions, a widely-documented occurrence that is commonly referred to as the theory of latitudinal gradient (Cross, Cross, & Piccio, 2012). A review by Handel et al. (2010) found additional evidence for environmental and geographical influences in the etiology of MS based on data from migration studies: Persons who emigrate during childhood assume the same prevalence risk as those of the new country. As stated in a review by Koch-Henriken and Sorensen (2010), the irregular distribution of MS across geographical populations can be attributed to differences in the interaction of genes and the environment; however, sources of error, such as prevalence and incidence surveys being affected by inaccuracy of diagnosis and data ascertainment, might play a part in the geographical and temporal variations found in MS.

Exposure to sunlight and/or vitamin D are suggested to be an important environmental factor(s) in the etiology of MS (less sunlight/vitamin D increasing MS risk), as well as possibly exposure to the Epstein-Barr virus (EBV) (Ascherio & Munger, 2007; Handel, Giovannoni, et al., 2010). Other, less definitive

evidence for environmental factors in the etiology of MS include smoking, physical trauma, respiratory tract infections, organic solvents and a fatty diet (Handel, Giovannoni, et al., 2010; Handel, Handunnetthi, et al., 2010; Milo & Kahana, 2010; Ramagopalan, Dobson, Meier, & Giovannoni, 2010), factors that are more frequently found in developed countries.

1.3. Diagnosis

The International Panel on MS-Diagnosis has created and recently (2010) revised guidelines termed the "Revised McDonald Criteria" for the diagnosis of MS (Polman et al., 2011). According to these guidelines, MS is diagnosed when a patient has experienced a minimum of two episodes of neurological disturbance that implicate spatially and temporally disseminated multifocal inflammatory demyelinated plaques in the CNS, while excluding other viable diagnoses. Although diagnosing MS can be made on the attainment of clinical evidence alone if the patient has experienced at least two separate episodes of CNS impairment, the use of MRI can further justify, augment or substitute clinical evidence to meet the diagnostic threshold (Polman et al., 2011). Cerebrospinal fluid (CSF) testing and/or evoked potential examinations can be used to diagnose MS as well. The full 2010 Revised McDonald Criteria are outlined in **Appendix A.**

1.4. Classification of MS-related disability

The MS disease course is marked by combination attacks of inflammation and degeneration that leads to brain and spinal cord damage/atrophy and associated functional deficits. As the disease evolves, the brain and spinal cord become increasingly deprived of sensory inputs and lose the ability to transmit signals as well. The most widely used scale for rating the level of neurological disability for MS patients is the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). The EDSS summarizes a patient's disability based on 8 functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other (miscellaneous). The EDSS typically rates the severity

level of disability with a major emphasis on the patient's ability to walk. For each functional system, a patient receives a clinical/qualitative rating on a 0-5 or 0-6 scale based on his/her performance on a neurological examination. The individual functional system ratings are then combined to give a total score (i.e., composite score) from 0-10, with 0.5 increments. An EDSS score of 0 denotes an unremarkable neurological examination, whereas an EDSS score of 10 denotes death. See **Table I-1** for a breakdown of each EDSS increment.

Table I-1. *Classification of disability associated with multiple-sclerosis according to the Expanded Disability Status Scale (EDSS; Kurtzke, 1983)*

EDSS Score	***Result of neurological examination/level of disability***
0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out

EDSS Score	*Result of neurological examination/level of disability*
	of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

FS: Functional system

While still widely used to classify stages of disease development and associated neurological impairment, the EDSS has also been criticized (Hobart, Freeman, & Thompson, 2000; Naci, Fleurence, Birt, & Duhig, 2010). Core points of criticism include the qualitative nature of the scale, insensitivity in higher ranges of disability, emphasis on the patient's ability to walk and inability to account for the cognitive or mood changes commonly associated with MS.

1.5. Multiple sclerosis subtypes

The MS disease course is capricious and initially difficult to predict. There are at least four different subtypes of MS used to categorize patients according to the course of their disease (Fox, R. J., 2010): relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive-relapsing MS (PRMS). These subtypes differ in clinical features, prognosis, and disease trajectories (see **Figure I-1**).

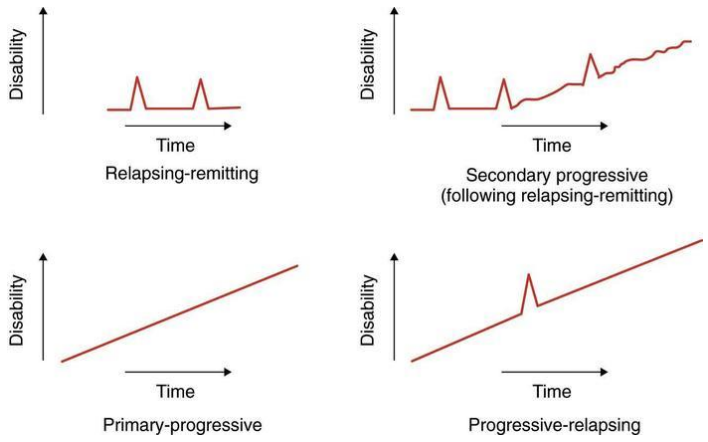

Figure I-1. *The clinical courses of the four different subtypes of MS* (Fox, R. J., 2010).

MS typically begins with a clinically isolated syndrome (CIS), an apparent neurological attack (e.g., optic neuritis) highly suggestive of inflammation/demyelination. Given that CIS is characterized by one (but not more than one) discrete neurological disturbance, CIS does not fulfill criteria for the diagnosis MS (Miller, D., Barkhof, Montalban, Thompson, & Filippi, 2005). Yet, approximately 30% to 70% of persons with a CIS later develop definitive MS. The majority (~85%) of patients with a diagnosis of MS have the RR subtype. RRMS is characterized by a biphasic disease course: acute episodes of neurological disruption (relapses) with variable recovery from a relapse that alternate with a stable course between attacks. Overall, with RRMS there is often minimal disease progression. However, over time, most RRMS patients evolve into the chronic phase of the disease (Feinstein, 2007; Noseworthy et al., 2000). Within 25 years, approximately 90% of RRMS patients advance into the SP disease course. SPMS is characterized by ceasing inflammatory activity but increasing and steady neurological decline (Feinstein, 2007; Noseworthy et al., 2000). RRMS tends to have an earlier onset compared to other subtypes of MS, averaging 25- 29 years; patients convert to a SPMS disease course at a mean age of 40-44 years (Feinstein, 2007; Noseworthy et al., 2000).

About 10% of MS patients exhibit a disease course with a rapid and steady decline in neurological function from disease onset, without ever experiencing recovery or remission periods, and are classified as having PPMS (Feinstein, 2007; Noseworthy et al., 2000). Patients following this disease course experience less frequent inflammatory responses; instead, axonal loss and GM and WM damage consistently increase, and eventually lends to greater disability (Feinstein, 2007; Noseworthy et al., 2000). PPMS has a mean age of onset of 35-39 years, this is nearly ten years later than RRMS patients (Feinstein, 2007; Noseworthy et al., 2000). A small minority of MS patients (~5%) suffer from a disease course characterized by progressive neurological decline accompanied with well-marked acute attacks (i.e., relapses) with very limited recovery. This disease course is classified as PRMS (Feinstein, 2007; Noseworthy et al., 2000).

Overall, less than 5% of MS patients have very severe disability within the first 5 years after onset, with 10–20% of patients remaining unimpaired without therapy after 20 years of the disease (Scalfari et al., 2010). In primary progressive forms of MS, the median time from disease onset to reaching irreversible disability is significantly earlier compared to RRMS, with most progressive MS patients having developed mild to moderate disability by the time they are diagnosed (Scalfari et al., 2010). Prior to disease-modifying therapies, the median time from disease onset to cane requirement was 15 years, disease onset to bedbound status was 26 years, and then disease onset to death was roughly 41 years (Scalfari et al., 2010). The degree that disease-modifying therapies (i.e., medications that exclusively act on the inflammatory activity of the disease and are therefore only useful in RRMS) alter this timeline of progression is still to be determined (Trojano et al., 2007). The median lifespan for MS patients is approximately 5–10 years shorter than for the age-matched general population (Bronnum-Hansen, Koch-Henriksen, & Stenager, 2004).

1.6. Pathophysiology and brain changes

The histopathology of MS is quite heterogeneous but classically comprises focal demyelination in the brain and spinal cord, initially linked to inflammation and edema, followed by axonal damage, loss of oligodendrocytes, microglial activation, and astroglial scarring (Filippi, Dousset, McFarland, Miller, & Grossman, 2002; Fisher, Lee, Nakamura, & Rudick, 2008). Myelin is a complex of lipoproteins made by oligodendrocytes that envelope the axon and aids in signal transmission. As MS progresses, acute viral or bacterial infections may result in a breakdown of the blood-brain-barrier (BBB), that then becomes permeable to T-cells and other lymphocytes and there is an increase of inflammatory attacks over time (i.e., attacking myelin as if body-foreign). Over time, myelin is degraded, becomes detached from the axon and eventually becomes phagocytosed by invading macrophages. This disruption in neural conduction results in clinical symptoms. Locations of active inflammation (lesions or plaques) are highly visible on structural MRIs (Filippi, Rocca, et al.,

2002). Neuroimaging and histological demonstrations of demyelination tend to reveal a periventricular distribution, although lesions can also be found amidst or adjacent to large WM tracts (e.g., Tiemann, Penner, Haupts, Schlegel, & Calabrese, 2009). Active and focal inflammatory lesions in the WM are more common in patients with acute or relapsing forms of MS, while in progressive forms of MS, there are more diffuse, non-active WM lesions, along with demyelination in the cortex and more progressive axonal injury (damage to the myelin and axon itself) (Kutzelnigg et al., 2005).

Importantly, it has now been accepted that WM lesion load (regardless of whether lesions are active or not) does not provide a comprehensive explanation of disease progression or (cognitive) impairment in MS (Barkhof, 2002). Although there have been fewer investigations of GM changes in MS, plaques in the GM can be observed in post mortem/tissue examinations of patients (Geurts, Stys, Minagar, Amor, & Zivadinov, 2009; Kidd et al., 1999). GM demyelination differs from WM demyelination whose pathological hallmarks (BBB breakdown, massive infiltration of lymphocytes and macrophages), are typically absent (Peterson, Bo, Mork, Chang, & Trapp, 2001). These findings suggest that different pathological mechanisms may drive GM and WM lesions in MS. There is evidence that cortical GM lesions can occur secondary to WM damage (Cifelli et al., 2002; Simon, Kinkel, Jacobs, Bub, & Simonian, 2000), but can also occur in independently (Bo, Geurts, van der Valk, Polman, & Barkhof, 2007). Thus, cortical GM could be an independent early and/or initial target of MS-related brain pathology. Even though the exact temporal and causal interplay between WM and GM changes in MS is currently unclear, it is suspected to differ between MS subtypes and different disease trajectories (Pirko & Johnson, 2008). Both types of MS-pathology are related to disease progression and cognitive deterioration and this will be outlined in the next section.

1.6.1. Brain changes in MS and their clinical/cognitive correlates

The most commonly assessed pathological brain changes, in conjunction with disability (usually EDSS) and cognitive impairment, are discrete, visible MS-specific WM lesions ("plaques" usually visualized by gadolinium enhanced T2-weighted MR imaging) and GM atrophy (global or regional), followed by cortical lesions (reflecting GM or mixed GM/WM lesions) and changes in WM integrity [diffuse damage to normal appearing white matter (NAWM) or tract-specific damage] using different MR imaging parameters. A comprehensive review of these findings is beyond the scope of this thesis. Therefore, the relationships between these parameters and disease severity as well as cognitive impairment will only be reviewed briefly before turning to global brain atrophy, as the latter was assessed in the current study.

A) White matter lesions: As mentioned above, WM lesions have long been known as a critical finding in MS. To quantify WM lesion load, visible WM lesions acquired through gadolinium enhanced T2-weighted MR image sequences are usually traced manually on MR images by a radiologist and their volume is calculated. Less detailed measures include simple lesion counts. Such WM lesions have sometimes been associated with disease severity and cognitive dysfunctions (Calabrese, M., Rinaldi, Grossi, & Gallo, 2011; Camp et al., 1999; Rao, Leo, Haughton, St Aubin-Faubert, & Bernardin, 1989; Ron, Callanan, & Warrington, 1991; Rovaris, Marco et al., 2000). However, mapping lesions to cognitive dysfunction is often relatively poor, leading to the formulation of a 'clinico-radiological paradox' in MS (Barkhof, 2002). If correlations are found between lesions and cognitive deficits, these can have regional specificity. For example, WM lesion burden in the frontal lobe was associated with executive dysfunctions in Arnett et al. (1994) and in Swirsky-Sacchetti (1992). More recently, Llufriu and colleagues (2012) found that even small damage to the structural integrity of the corpus callosum (the major WM commissural tract in the brain) correlated with dysfunction in verbal and visual memory, information processing speed and executive tasks. The frequency of lesions in the corpus callosum was lower in

cognitively intact than in cognitively impaired MS-patients (especially in patients who showed deficits on a test of processing speed) in Rossi et al. (2001). Since WM lesions are often located in periventricular brain regions, and increasing degeneration in those areas could interrupt WM tracts that originate from or project to prefrontal, cingulate, and association areas (Bendfeldt et al., 2012), WM lesions might lead to functional disconnection of cortical areas and deep GM structures that are critical for many cognitive and sensory functions (e.g., the thalamus). In addition, the periventricular anterior cingulate gyrus has extensive connections with many cortical regions including the insula, which, in turn has numerous connections with the limbic system, (e.g., the hippocampus, parahippocampal gyrus), as well as the frontal, parietal and temporal cortices (Charil et al., 2007). Histopathological studies in MS have demonstrated that these areas are more demyelinated than others (Kutzelnigg et al., 2005).

B) Gray matter atrophy: Changes in GM are usually not assessed manually but are based on (customized) automated segmentation procedures, producing volumetric measures of all GM within each 3D voxel of brain tissue. Several research groups confirmed that the relationship between cognition and GM atrophy often supersedes that with WM lesions in MS (Bakshi, Benedict, Bermel, & Jacobs, 2001; De Stefano et al., 2003; Sanfilipo, Benedict, Sharma, Weinstock-Guttman, & Bakshi, 2005). Thus, GM damage (diffuse or focal) is not only more prevalent in MS than initially thought (Brownell & Hughes, 1962; Calabrese, M., Rocca, et al., 2009; Calabrese, M., Rocca, et al., 2010; De Stefano et al., 2003), but quite significantly related to cognitive impairment (e.g., Amato et al., 2004; Amato & De Stefano, 2007; Calabrese, M., Rinaldi, Mattisi, et al., 2010; Tekok-Kilic et al., 2007). Subcortical (‘deep’) GM damage is common in MS (Bermel, Innus, Tjoa, & Bakshi, 2003; Cifelli et al., 2002; Prinster et al., 2006; Sepulcre et al., 2006). Among affected sites are the thalamus and basal ganglia, followed by hypothalamus, hippocampus, cerebellum and spinal cord (Calabrese, M., Mattisi, et al., 2010; Gilmore et al., 2006; Vercellino et al., 2005). Among these sites, the most robust and consensual finding for correlation between cognition and GM

atrophy is found with the thalamus (Batista et al., 2012; Benedict et al., 2013; Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2009; Houtchens et al., 2007).

Cortical GM atrophy is most pronounced in temporal and frontal cortex (including motor cortex), and parallels impairment in motor, memory and executive functions (Benedict, Zivadinov, et al., 2005; Chen et al., 2004; De Stefano et al., 2003; Fisher et al., 2008; Morgen et al., 2006; Prinster et al., 2006; Tekok-Kilic et al., 2007). Changes in GM are closely associated with both physical disability and its progression (correlations range from r= 0.47-0.59) (Bonati et al., 2011; Chen et al., 2004; Fisher et al., 2008; Fisniku et al., 2008; Horakova et al., 2009) as well as cognitive impairment (Amato et al., 2007; Calabrese, M., Agosta, et al., 2009; Calabrese, M., Rocca, et al., 2010; De Stefano et al., 2003; Sanfilipo et al., 2005; Tekok-Kilic et al., 2007). A recent meta-analysis (Lansley, Mataix-Cols, Grau, Radua, & Sastre-Garriga, 2013) found that MS-related GM reductions across 19 studies and 500 RRMS patients were rather regionally-specific and involved bilateral thalamus, basal ganglia structures, pre/postcentral cortex and cingulate gyrus. Disability (EDSS) was related to atrophy in pre/postcentral gyrus regions only; according to the authors, likely as a result of the bias in the EDSS towards assessing locomotor disability. Cognition was not assessed in this meta-analysis.

Fisniku and colleagues (2008) showed that GM atrophy, unlike WM atrophy, increases in patients with moderate disability (EDSS> 3). This view is further supported by findings that the rate of GM atrophy is accelerated upon conversion from CIS to the RRMS and SPMS (3.4× and 14× the normal rates, respectively), while WM atrophy remains relatively stable throughout the same MS courses (3× the normal rate) (Dalton et al., 2004; Fisher et al., 2008). Thus, GM pathology may better represent progressive CNS damage and resulting physical disability in MS patients than WM pathology, although some contrasting results have also been reported (Sastre-Garriga et al., 2004).

Of note, cognitive impairment is more prominent during the time that the MS disease course converts from a RR subtype to the SP type (Benedict, Carone, & Bakshi, 2004; Filippi et al., 1994); this also happens to be a time marked with accelerated degeneration of the cerebral GM (Fisher et al., 2008).

C) Gray matter lesions: Apart from GM atrophy, cortical and subcortical inflammatory GM lesions also contribute to overall disability in MS (Hayton et al., 2009; Rovaris, M., Judica, et al., 2008). These types of lesions have been less well studied, but they seem to show mild correlation with current EDSS scores and moderate correlation with EDSS changes over time (Calabrese, M., Rocca, et al., 2010). Similar to GM atrophy, PPMS patients show more pronounced accumulation of active GM lesions, paralleling increased physical disability (Calabrese, M., Rocca, et al., 2009). It was suggested that fatigue in MS patients could be secondary to the regional atrophy of the fronto-parietal cortex, striatum and thalamus (Calabrese, M., Rinaldi, Grossi, et al., 2010; Filippi, Rocca, et al., 2002; Niepel et al., 2006) as well as the higher overall GM lesion burden (Riccitelli et al., 2011; Sepulcre et al., 2009). Yet, it is not known whether the severity of physical impairment is proportional to GM lesion volume or whether it depends more on the topography of the GM lesions (see Horakova, Kalincik, Dusankova, & Dolezal, 2012 for more detailed discussion).

D) Changes in white matter integrity: As mentioned above, in addition to visible MS-specific WM lesions, diffuse WM damage in "normal appearing white matter" (NAMW) as well as tract-specific WM changes are also common in MS (Filippi et al., 2000; Ge, Law, & Grossman, 2005; Guo, Jewells, & Provenzale, 2001). Both pathologies have been related to disability and cognitive impairment in numerous studies (Lin, X., Tench, Morgan, Niepel, & Constantinescu, 2005; Ozturk et al., 2010; Preziosa et al., 2011; Wilson, Tench, Morgan, & Blumhardt, 2003). For example, diffusion-tensor imaging (DTI)-based tractography of the corpus callosum was sensitive to changes in processing speed in Lin et al. (2008), similar to a study from Yu and others (2012), who found the strongest correlations

between information processing speed and DTI-measures of WM disintegration (lesions, NAWM volumes) in the thalamic radiation, corpus callosum and the sagittal stratum (an occipito-temporal white matter tract).

Comparing the relative contributions of the type of MRI-based in vivo brain pathology to disease severity and cognition is complicated and studies often yield inconsistent results. For example, Penny et al. (2010) showed in a longitudinal study in PPMS patients that baseline WM lesion volume was the best MRI predictor of overall cognitive function, verbal memory and attention/speed of information processing after 5 years. In line with this finding, Bagnato et al. (2010) found cortical GM lesions to be related to cognitive impairment in 21 MS patients, but this correlation was rendered insignificant when WM lesion load was controlled, suggesting no contributions of GM lesions over and above effects of WM lesions to explain cognitive deficits in this study. Hulst and colleagues (2013) compared diffuse WM pathology, discrete WM lesions, and GM atrophy in conjunction with cognition in 55 MS patients. They found only *diffuse* WM structural changes (assessed with DTI) to be related to cognitive deficits in patients. Calabrese et al. (2009) found that cognitive impairment across 70 MS patients was independently predicted by cortical lesions and regional GM atrophy, but not by WM lesions. A more recent longitudinal study by the same group in 312 patients, however, found that cortical lesion volume, GM fraction as well as T2-WM lesion volume at baseline were all independent predictors of cognitive status after a five year follow-up (Calabrese, M. et al., 2012).

Much of the contradictory evidence is likely due to differences in the assessment of and focus on particular pathological brain changes, the size of the effects and therefore power-issues with smaller sized studies, as well as different imaging parameters and associated sensitivity for any particular brain pathology across studies. It can be reasonably assumed that all pathological changes contribute to MS-related disability and cognitive disturbance although the exact extent that they do so is difficult to quantify and definitively determine across studies.

E) Global atrophy measures: In addition to specific WM or GM pathology, whole brain or regional atrophy are also commonly associated with the presence of cognitive dysfunction, since they encompass both WM and GM pathologies in MS. For example, brain atrophic changes may better explain cognitive impairment in RRMS patients than WM lesion volume alone (Morgen et al., 2006; Sanchez, Nieto, Barroso, Martin, & Hernandez, 2008). One study reported that global brain atrophy in MS accounts for about 10-15% of the variance in verbal learning and memory tasks and about 33% in processing speed tasks (Benedict, Bruce, et al., 2006). Several other MRI studies have demonstrated that global corpus callosum and frontal lobe atrophy provide robust correlates of MS-associated cognitive dysfunction (Benedict, Carone, et al., 2004; Rovaris, M., Comi, & Filippi, 2006; Zivadinov, De Masi, et al., 2001; Zivadinov, Sepcic, et al., 2001).

A relatively simple method of estimating brain atrophy is achieved via linear 2-dimensional (2D) measurements, included in the current study. These linear measurements can be performed on structural MRI to provide gross information on overall brain atrophy in patients. The benefits of such linear measurements are that they are simple and rapid, and that they can be performed on standard clinical MR scans that are available for most patients. Compared to modern MR imaging techniques developed to detect MS-specific brain pathologies, evidently, linear atrophy measures are relatively crude and variability between scanners and scan sequences across centers will influence the results. Nevertheless, atrophic changes that can be linked to disease progression and cognitive decline in MS have used this approach and these are outlined below.

1.6.2. Linear measurements of structural MRIs in MS

Linear measures of the width of the brain, corpus callosum and the ventricles have been applied in MS for decades. Four commonly used linear measurements include that estimate ventricular size are: Frontal horn width (FHW; Berg, D., Maurer, Warmuth-Metz, Rieckmann, & Becker, 2000;

Butzkueven et al., 2008; Martola et al., 2008; Simon et al., 1999), third ventricle width (TVW; Berg, D. et al., 2000; Butzkueven et al., 2008; Martola et al., 2008; Simon et al., 1999), intercaudate nucleus distance (ICD; Butzkueven et al., 2008) and intercaudate ratio (ICR; Bermel, Bakshi, Tjoa, Puli, & Jacobs, 2002; Butzkueven et al., 2008). Indicators of ventricular enlargement reflect a loss of brain parenchyma (Fox, N. C. et al., 2000; Turner, Lin, Calmon, Roberts, & Blumhardt, 2003), in particular, reductions in thalami, basal ganglia, and periventricular WM, structures that form the walls of the third and lateral ventricles (Martola et al., 2008). Ventricular enlargement can be found within one year of disease duration in MS and continues as the disease progresses, even after over 4 decades (Martola et al., 2008).

After visually selecting the appropriate slice position for each assessment, the linear distances of each structure/region is obtained from a 2D single-image axial slice using a linear distance tool. A validation study by Butzkueven and colleagues (2008) tested three linear markers of ventricular enlargement, ICD, TVW and FHW, against results of an automated protocol used to assess brain parenchymal volume (Butzkueven et al., 2008). The TVW ($p=0.001$) and ICD ($p<0.001$) measures differentiated well between MS cases and controls. Ratio measurements based on TVW and ICD that also take into account skull size inversely correlated with brain parenchymal volume ($p<0.01$) cross-sectionally and after 4 years time (Butzkueven et al., 2008). Turner and colleagues (2001) also validated that some linear measurements correlate well with 3-dimensional (3D) ventricle volumes (Turner et al., 2001). In this study, TVW showed the strongest association with the clinical stage of the disease (i.e., disease duration, duration of symptoms and disability). These studies show that linear measurements obtained from clinical MRI scans can indeed validly estimate brain atrophy in MS.

MS lesions and atrophy in GM structures surrounding the third ventricle may disrupt WM tracts interconnecting prefrontal-limbic structures, resulting in MS-characteristic deficits of memory and "frontal" functions (Rao, 1986). The

size of third ventricle estimates the volume of the thalamus, a region that is an important hub for mediating cognitive deficits in MS (Batista et al., 2012; Benedict et al., 2013; Benedict et al., 2009; Houtchens et al., 2007). TVW has been more strongly related to cognitive deficits compared to measures of lesion load and global brain volume in several studies (Benedict, Bruce, et al., 2006; Benedict, Weinstock-Guttman, et al., 2004; Tekok-Kilic et al., 2007). TVW has been found to be an indicator of significant disease progression, for example in RRMS patients (Simon et al., 1999). In addition, ICD and ICR (i.e., ICR accounting for skull size) are thought to reflect atrophy of WM tracts and ventricular enlargement near the basal ganglia, especially the caudate nuclei (Bermel et al., 2002). Both measures, especially the ICR, were found to relate to severity, duration, as well as cognitive deficits, especially deficits in processing speed in MS (Bermel et al., 2002; Butzkueven et al., 2008; Caon et al., 2003). However, it is important to note that 2D linear measures sometimes (Martola et al., 2008; Turner et al., 2001), but not always, correlate with disease duration or EDSS (Clark, C. M. et al., 1992; Kalkers et al., 2002).

In summary, linear measures of ventricular enlargement can be understood as approximations of brain atrophy in MS. Similar to more sophisticated 3D measures, they have previously been related to disease severity, progression and cognitive dysfunction in MS in several studies. Although precision and replicability of these measures are necessarily inferior to 3D volumetric measures, their ease of implementation as well as the wide availability of clinical MR scans in MS patients are attractive features of 2D linear measures. Two-dimensional linear measures were used in the current study.

1.7. Cognition in MS

Although descriptions of altered mentation in MS were noticed long before Jean-Martin Charcot, the French neurologist, came to name this condition (Charcot, 1868), only since the mid-1980s have greater efforts been invested towards testing MS-associated behavioral and cognitive changes. Early research

into the psychological and cognitive aspects of MS focused on an undifferentiated category of "mental symptoms" (fatigue, sleep, emotional and cognitive problems) that were initially considered secondary to the more overt physical symptoms assumed to be most debilitating. However, with improved psychometric methodologies, cognitive deficits are now recognized as a primary and often intensely disabling aspect of MS. Cognitive impairment is present in nearly half of all MS patients, with prevalence rates ranging from 43 to 70% (Amato, Zipoli, & Portaccio, 2008; Chiaravalloti & DeLuca, 2008; Ferreira, 2010). Cognitive impairment can be difficult to detect because it is only mildly associated with physical impairment (Beatty, Goodkin, Hertsgaard, & Monson, 1990; Piras et al., 2003), can occur at any stage of the disease, and may not directly covary with disease duration (Beatty et al., 1990). Although cognitive impairment can even present in the very beginning of the disease (Achiron & Barak, 2003; Deloire et al., 2005; Feuillet et al., 2007; Glanz et al., 2007; Potagas et al., 2008; Zipoli et al., 2010), cognitive disturbances are usually more severe in patients with SPMS compared to those in the RR stage (Beatty et al., 1990).

MS-related cognitive impairment has detrimental effects on activities of daily living (e.g., grocery shopping, driving, banking), autonomy, and social activities and interactions (Chiaravalloti & DeLuca, 2008). Additionally, the presence of cognitive deficits accounts for more variance in employment status (Chiaravalloti & DeLuca, 2008) than physical disability and demographic factors associated with the disease (Larocca, Kalb, Scheinberg, & Kendall, 1985). Therefore, it is safe to assume cognitive deficits considerably reduce the quality of life of MS patients and should be of primary concern in this disorder (Chiaravalloti & DeLuca, 2008; Rao, Leo, Bernardin, & Unverzagt, 1991).

1.7.1. Neuropsychological assessment of cognition in MS

MS patients' self-report of their cognitive impairments, although important clinically, is not always reflective of their true cognitive performance, but might be instead linked to changes in mood such as depression (Langdon, 2011). Therefore, objective neuropsychological measurement of cognitive abilities is

desirable. Neuropsychological assessment involves the formal use of standardized tests to appraise the extent of impairment of cognitive function(s) with respect to normative performance of a healthy age- (and education-) matched general population. Historically, neuropsychological assessment was aimed at localizing an area of the brain presumably affected by neurological illness or injury. Since the localization of MS-related brain changes is non-focal and diffuse, a variety of cognitive functions can be impaired in MS. Frank dementia (global cognitive decline) is rare in MS (Amato et al., 2010); instead, more subtle cognitive deficits, that can vary substantially among patients (Chiaravalloti & DeLuca, 2008) are more often observed. In general, areas of cognitive impairment in MS include the efficiency and speed of information processing, verbal and visual-spatial memory, attention, visual perceptual processing, and executive functioning. Processing speed/attention and memory are the hallmark cognitive domains with deficits in MS (Benedict, Cookfair, et al., 2006; Rao et al., 1991). A brief summary of aspects of impaired cognition in MS is given in the following.

A) Information processing speed. Information processing speed refers to the speed and capacity that one can sequence and execute cognitive information. Reduced speed of information processing is considered the single most common cognitive deficit in MS, affecting nearly half of all patients (Denney, Lynch, & Parmenter, 2008; Rao et al., 1991). Compared to controls, generalized slowing in information processing is greater in progressive subtypes (50% slower) than in RRMS (24% slower). Deficits in processing speed emerge even when controlling for motor involvement can be demonstrated by auditory tests requiring no motor output (De Sonneville et al., 2002). MS patients' slowed processing speed is even more pronounced on tasks that are explicitly timed (Denney, Gallagher, & Lynch, 2011). However, when cognitive load is reduced, by increasing the interval between stimulus presentation and the allotted time to respond, there is an improvement in the accuracy of MS patients' performance (Leavitt, Lengenfelder, Moore, Chiaravalloti, & DeLuca, 2011). Over several years, MS patients'

performance on tests of information processing speed declines more rapidly than that on other cognitive tests (Denney et al., 2008).

B) Attention. Attention involves selecting a (sub)set of information to focus on for enhanced processing and can include a single information source or several sources. Attention often involves processing speed and working memory. Complex aspects of attention (e.g., selective and divided attention) are most often impaired, whereas simpler forms (e.g., attention span) are generally intact in MS patients (Amato, Zipoli, et al., 2008). Impaired attention and reduced information-processing speed represent the most sensitive indicators of incipient cognitive dysfunction in MS (Amato, Zipoli, et al., 2008).

C) Memory. Memory refers to the ability to learn new information and to recall that information after a delay. Besides processing speed/attention, learning and memory deficits are considered one of the most frequent cognitive problems in MS, affecting between 40-60% of all patients (Calabrese, P., 2006). Within long-term memory, the formation of new episodic memories [declarative memory (Squire & McKee, 1993); i.e., memory for materials that the individual has been instructed to learn and that they can then verbally retrieve/'declare'] is frequently affected. For example, when learning a list of words, MS patients are slower at acquiring information over multiple trials and have difficulty organizing words in semantically logical groups that facilitate recall, especially if the words are unfamiliar (Rao, Hammeke, McQuillen, Khatri, & Lloyd, 1984). Conversely, semantic memory (i.e., memory for time-unspecific and over-learned information such as the meaning of words or symbols) as well as implicit memory (learning and remembering that happens without conscious awareness) are usually preserved in MS patients (Amato, Zipoli, et al., 2008). Short-term or "working memory" (the ability to maintain and manipulate a limited set of information over a brief period of time) is also commonly impaired in MS; however, when recalling a short span of numbers (i.e., Forward Digit Span), patients may perform similar to controls (Rao, Leo, & St Aubin-Faubert, 1989). Ultimately, long-term

episodic memory is one of the most consistently impaired cognitive functions in MS (Rao, Reingold, Ron, Lyon-Caen, & Comi, 1993). Memory deficits also serve as an indicator of daily functioning in MS (Higginson, Arnett, & Voss, 2000).

D) Visual abilities. Visual perceptual processing includes simple recognition of visual stimulus characteristics (e.g., characteristics of faces, identification of visual forms and visual-spatial orientation of objects) and the ability to remember and manipulate their location and orientation. Visual abilities are impaired in over 20% of MS patients (Benedict & Zivadinov, 2006). Difficulties in primary visual processing (e.g., from optic neuritis) in MS can have a detrimental effect on visual perception processes, although perceptual deficits that are independent of primary visual or other cognitive abnormalities can also occur. In general, impairments in this domain can be seen in visual-perceptual tasks such as Judgment of Line Orientation (distinguishing the planes/degree of angle a straight line is presented at), in facial recognition and in tasks that require identifying previously-seen complex objects (Rao et al., 1991). Since perception is the first step to further and more complex cognitive processes, impairments in visual processing might also lead to a decreased performance in tasks of processing speed, motor abilities as well as memory (Vleugels et al., 2000).

E) Executive functions. "Executive functions" is an umbrella term referring to higher-order cognitive abilities needed for complex goal-directed behavior and flexible adaptation to environmental changes or demands (Miyake et al., 2000). There is considerable debate about the exact nature and definition of executive functions, a debate that is beyond the scope of the current thesis (see Fournier-Vicente, Larigauderie, & Gaonac'h, 2008; Miyake et al., 2000; Royall et al., 2002). Classically, executive functions include the ability to plan, anticipate outcomes, monitor one's own behaviour, flexibly shift mental sets and direct one's own cognitive processing resources appropriately. Classic executive dysfunctions found in MS patients involve abstract reasoning, problem solving, planning, monitoring and cognitive estimation (Amato, Zipoli, et al., 2008).

Additional executive dysfunctions, such as disinhibition, the ability to shift sets, and poor fluency, were found to be as common as 17% in one MS sample of mixed subtypes (Drew, Tippett, Starkey, & Isler, 2008). MS patients may show deficits in phonemic and semantic verbal fluency tasks, not as a reflection of their language abilities, but because fluency tasks, especially phonemic fluency, also recruit/assess executive functions (e.g., Henry, J. D. & Crawford, 2004). Deficits in executive functioning are most pronounced in patients with SPMS and PPMS (Rao et al., 1991). Approximately 15- 20% of MS patients show deficits in one or more executive function (Drew et al., 2008; Rao et al., 1991).

F) Language Abilities. Language abilities are typically measured with naming, comprehension, reading, fluency and writing tasks. Most linguistic abilities are usually preserved in MS patients (Jennekens-Schinkel, Lanser, van der Velde, & Sanders, 1990; Merson & Rolnick, 1998); however, tests of verbal, category or semantic fluency reveal deficits as compared to controls (Friend et al., 1999). Weaknesses in sentence comprehension have been linked to slowed information processing (Grossman et al., 1995). In tasks of verbal fluency, 13-23% of patients are demonstrating borderline or greater impairment (Benedict & Zivadinov, 2006; McIntosh-Michaelis et al., 1991; Rao et al., 1991). As mentioned above, deficits in fluency are often related to impairment in other cognitive domains, such as executive functions and speed of processing, and this is true for MS patients as well (Friend et al., 1999).

G) Intelligence. Intelligence (also referred to as IQ: intelligence quotient) can be assessed with complex, multi-subtest batteries (e.g., the Wechsler Adult Intelligence Scale, [Wechsler, 1997]), yielding comprehensive measures of crystallized (using non-timed, education-dependent and age-resistant tasks) and fluid intelligence (using speeded, relatively education-independent, but age-sensitive tasks). Crystallized intelligence also tends to be more resistant to the detrimental effects of cerebral pathology than abilities associated with fluid intelligence. Therefore, in clinical studies, premorbid (i.e., pre-illness) intelligence

(premorbid IQ) is often estimated with tests of crystallized intelligence such as reading, vocabulary or word pronunciation/comprehension tests, which are thought to capture stable abilities based on the lifetime acquisition of semantic knowledge. In MS patients, premorbid IQ is usually normal, or shows only a moderate decline as the disease progresses (Amato, Zipoli, et al., 2008), unless in cases of incipient cognitive decline, when performance-based measures of intelligence (i.e., spatial skills) can decrease more steeply (Kujala, Portin, & Ruutiainen, 1996). Paralleling findings in normal aging with those in aging patient populations, MS patients with higher premorbid IQ demonstrate greater cognitive resilience, a finding that applies to both RRMS (Sumowski, Chiaravalloti, & DeLuca, 2009) as well as SPMS patients (Sumowski, Chiaravalloti, Leavitt, & Deluca, 2012). More specifically, higher premorbid IQ allowed RRMS patients to maintain a higher level of cognitive functioning in the face of increasing brain atrophy compared to those with lower premorbid IQ (Sumowski et al., 2009).

As summarized above, MS-related cognitive deficits frequently apply to specific cognitive domains, despite considerable diversity among patients in the presence and severity of such deficits. While comprehensive neuropsychological testing is certainly desirable and renders detailed recommendations for treatment and rehabilitation, factors such as the intensive testing time (4-6 hours) and the required reporting knowledge, significantly limit the likelihood of comprehensive neuropsychological testing to be part of routine practice in public health systems. However, a few neuropsychological screening batteries, aimed at assessing MS-specific deficits, have been generated. The two most widely used are outlined briefly here: The Brief Repeatable Battery of Neuropsychological Tests (BRB-N; Rao, 1990), and the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2002). The tests included in these batteries were largely selected for qualities such as: 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 tests included in these batteries and the administration times are presented in **Table I-2.**

Table I-2. *Summary of two neuropsychological screening batteries commonly used to detect cognitive deficits in MS*

	COGNITIVE DOMAINS TESTED						
Battery Name	**Processing Speed & Attention**	**Processing Speed & Working Memory**	**Verbal Learning/ Memory**	**Visual Learning/ Memory**	**Verbal Fluency**	**Executive Functions**	**Perception**
Brief Repeatable Battery of Neuropsychological Tests (BRB-N) *30 minutes*	Symbol Digit Modalities Test (SDMT)	Paced Auditory Serial Addition Test (PASAT)	Selective Reminding Test (SRT)	10/36 Spatial Recall Test	Word List Generation test (WLG)	-	-
Minimal Assessment of Cognitive Function in MS (MACFIMS) *90 minutes*	Symbol Digit Modalities Test (SDMT)	Paced Auditory Serial Addition Test (PASAT)	California Verbal Learning Test-II (CVLT-II)	Brief Visual Memory Test-Revised (BVMT-R)	Controlled Oral Word Association Test (COWAT)	Card Sorting Test from D-KEFS	Judgment of Line Orientation (JLO)

As can be seen in **Table I-2**, many tests overlap between the two batteries, with the PASAT (Gronwall, D. M., 1977), SDMT (Smith, A., 1982) and tests of verbal fluency (i.e., WLG and COWAT [Loonstra, Tarlow, & Sellers, 2001]). Of note, my current selection of neuropsychological tests was based on consideration of the tests included in these screening batteries as well as with the increased focus on the assessment of executive functions in my study. The details of my test battery will be described in the Methods section.

1.8. Neuropsychiatric changes in MS

Besides cognitive deficits, MS is associated with a number of neuro-psychiatric and vegetative changes. Specifically, fatigue is very common in MS and affects more than 70% of all patients (Hadjimichael, Vollmer, & Oleen-Burkey, 2008; Krupp, Alvarez, LaRocca, & Scheinberg, 1988). Furthermore, up to 50% of MS patients have comorbid depression (Feinstein, 2011; Jones, K. H. et al., 2012; Paparrigopoulos, Ferentinos, Kouzoupis, Koutsis, & Papadimitriou, 2010; Patten, Beck, Williams, Barbui, & Metz, 2003). Depression significantly influences quality of life in individuals with MS (Benedict, Wahlig, et al., 2005)

and the elevated prevalence of depression in MS poses important implications for the prevention of suicide in this disorder (Feinstein, 2002). As suggested by Arnett and colleagues, although disease-specific correlates (i.e., lesion load, brain atrophy) and direct symptoms of the disorder (fatigue, degree of physical impairment, cognitive dysfunctions, pain) will increase the risk for depression in MS, this link is likely moderated by the presence of stress (i.e., psychosocial, financial, health), the nature of stress coping styles and the level of social support (Arnett, Barwick, & Beeney, 2008). Although less systematically studied, anxiety disorders affect between 25% and 50% of MS patients (Feinstein, 2007; Jones, K. H. et al., 2012; Wood et al., 2012). Interestingly, a number of recent studies also found selective emotional processing deficits in MS including disturbed recognition of facial emotion and deficits in Theory of Mind (Banati et al., 2010; Henry, A. et al., 2011; Krause et al., 2009; Passamonti et al., 2009). Since the target neuropsychological function in my study is decision making, a function that comprises both cognitive and emotional elements, I was mindful to include a number of scales assessing the presence of common neuropsychiatric changes in MS. The details of these scales are given in the Methods section (**Section II-2**).

2. Decision making

Decision making is a complex process that requires an individual to form preferences, select and execute goal-driven actions, and evaluate the outcome related to choices (Ernst & Paulus, 2005). Decision making has a ubiquitous role in daily life. From the decision to start, continue, or stop eating chips in front of the TV to the decisions an individual makes about what college to attend and whether or not spending a night out with friends will help towards that specific aim, decision making tends to require both cognitive and emotional abilities. Cognitive abilities, more specifically, executive functions, such as categorization, task monitoring, set-shifting and cognitive flexibility, contribute to the deliberate and strategic aspects of decision making. However, in addition to executive functions, decision making also involves emotional aspects as it requires, for example, the fundamental capacity to perceive and appreciate reward/punishment

and the use of such feedback from past decisions to guide future decisions. Thus, making self-advantageous decisions requires both intact cognitive and emotional functioning, as each play a distinct but integral role in this self-regulatory behavior.

2.1. Types of decision making: Ambiguity vs. Risk

Most decision making situations offer more than one decision alternative. As a result, when trying to make the most appropriate choice, individuals have to perceive and evaluate the beneficial and detrimental consequences that are associated with the different options. Based on how explicit the likely consequences of the choice options are (i.e., how calculable the probability of reward or punishment is), decisions can be classified as decisions under ambiguity and decisions under risk.

"Decisions under ambiguity" (Bechara, 2004) refer to situations when the consequences of the decision are undefined and when there is no information provided about the likelihood of positive or negative consequences as an outcome of each choice. As a result of ambiguous decision situations, it is very difficult for the individual to consciously develop a decision strategy; instead, individuals are thought to "implicitly" rely on their own feelings, hunches and subtle emotional signals to help them make a decision (in accordance with the 'somatic marker hypothesis'; see (Damasio, A., 2004; Damasio, A. R., 1994; Damasio, H., Grabowski, Tranel, Hichwa, & Damasio, 1996; Damasio, H., Kuljis, Yuh, van Hoesen, & Ehrhardt, 1991). An example of a decision under ambiguity is being sick and then given the choice to opt in for a new treatment, but the probability that the treatment will improve your health is unknown (Brand, Recknor, Grabenhorst, & Bechara, 2007).

Conversely, many decisions can be made on the basis of some knowledge about the situation: the consequences are specified and the associated probabilities are explicitly known and quantifiable. These types of decisions are commonly referred to as "decisions under risk" (Brand, Labudda, & Markowitsch, 2006). An

example of a decision under risk would be when that sick patient is offered a new medication, and is also told the treatment has a 95% chance of success and a 5% chance of fatal complications (Brand, Recknor, et al., 2007).

Both, decision making under ambiguity and under risk continue to receive great attention in neuropsychological research. Impaired decision making is a symptom of many psychiatric, neurodegenerative and neurological diseases (see below). Two common tasks to assess neuropsychological decision making deficits in patient populations are the Iowa Gambling Task (IGT) and the Game of Dice Task (GDT).

2.1.1. Decisions under ambiguity: Iowa Gambling Task (IGT)

The Iowa Gambling Task (IGT) has been the first and continues to be the most common tool to assess decision making in patient populations. The IGT assesses decision making under ambiguity (Bechara, Damasio, Damasio, & Anderson, 1994) (see **Figure II-1**).

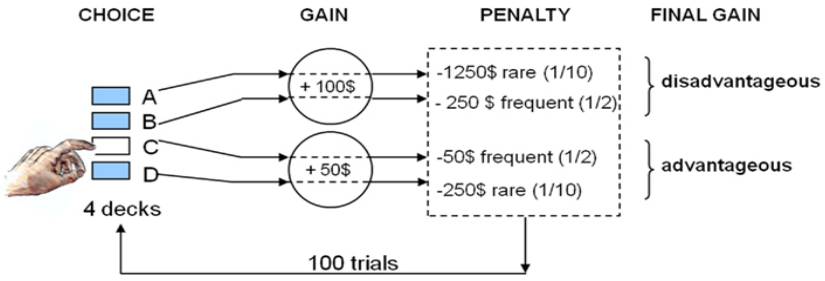

Figure II-1. *Schematic of the Iowa Gambling Task* (from (de Visser et al., 2011).

In the IGT, individuals are asked to choose a card from one of four card decks displayed on a computer screen (A, B, C, D). Participants are told that each time they choose a card they will win some game money, but every so often, choosing a card will cause them to lose some money. Unknown to the participant, two of the decks (A, B) are associated with short-term high gains (fictitious money wins) but even higher long-term losses. Decks A and B are referred to as "disadvantageous decks". The two other decks C and D are associated with low

gains but also with low losses and are referred to as "advantageous decks". The decks within each category (A vs. B and C vs. D) differ from each other in the percentage of loss to total trials (see **Figure II-1)**. The (explicit) goal of the IGT is to win as much money as possible. Over the course of 100 choice trials (with a 20-30 administration time), individuals are supposed learn to prefer the advantageous decks (C, D) and to avoid the disadvantageous decks (A, B). Importantly, individuals are not told about the probabilities of winning/losing or the number of trials in this task. Therefore, the IGT measures decision making under ambiguity, requiring implicit learning of advantageous/disadvantageous decks through the processing of feedback (i.e., perception and evaluation of subtle emotional signals about the value and consequence of one's own previous decisions) that occurs over many trials.

Healthy individuals tend to choose cards predominantly from the advantageous decks after approximately 40 card choices (equalling two 20-trial task blocks). The IGT produces a total "net-score" (number of advantageous minus disadvantageous choices) that is reported usually along with net-scores for each block of 20 cards/trials.

Poor performance in the IGT can be found in patients with substance and behavioural addictions, obsessive-compulsive disorder, schizophrenia, anorexia nervosa, suicide attempters, and other individuals suffering from neuropsychiatric symptoms (see extensive review by (Dunn, Dalgleish, & Lawrence, 2006a). The IGT is a relatively complicated task and its high sensitivity to detecting decision making deficits is limited by its relatively low specificity for the neural processes underlying decision making deficits (Brand, Recknor, et al., 2007). The initial motivation for the development of the IGT came from patients with relatively focal orbitofrontal/ ventromedial prefrontal cortex (OFC/VMPFC) lesions. These patients demonstrated impaired psychosocial functions, but showed normal executive functions such as in the Wisconsin Card Sorting Test (WCST), a task that is thought to rely on DLPFC rather than VMPFC integrity (Lie, Specht, Marshall, & Fink, 2006; Lombardi et al., 1999). Patients with lesions to the

OFC/VMPFC were indeed severely impaired in the IGT (Bechara et al., 1994; Bechara, Damasio, Tranel, & Anderson, 1998; Bechara, Tranel, & Damasio, 2000; Manes et al., 2002).

Patients with lesions including limbic structures, primarily those with amygdala (AMG) damage, also perform worse than healthy individuals on the IGT (Bechara, Damasio, Damasio, & Lee, 1999; Brand, Recknor, et al., 2007). The AMG links emotional information with sensory features (e.g., via early sensory and association cortices) with current autonomic reactivity, in decision making situations, sensations resulting from one's choice. Thus, the AMG becomes involved in tasks like emotional conditioning, the IGT, where risk-reward contingencies are encoded based on their ability to trigger an emotional response to wins or losses (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998). In the case of the IGT, AMG lesions result in depressed psychophysiological responding to the choice feedback (Bechara et al., 1999). Evidence from both focal OFC/VMPFC and AMG lesion patients, both of whom are impaired in the IGT, corroborates the importance of intact anticipatory and reward-related emotional processing in decision making in the IGT (e.g., Bechara, Damasio, & Damasio, 2003; Bechara, Damasio, Tranel, & Damasio, 1997, 2005; Brand, Franke-Sievert, Jacoby, Markowitsch, & Tuschen-Caffier, 2007). Further evidence comes from studies with the IGT that included a concurrent measurement of skin conductance responses (SCRs; a physiological indicator of emotional arousal). In such studies, healthy individuals display a temporary increase in SCR, a stress reaction, prior to choosing a card from the disadvantageous card decks (A, B) even after only 10 trials, i.e., long before they are consciously aware that these decks may be disadvantageous (Bechara et al., 1997). Patients with OFC/VMPFC dysfunction never develop this physiological reaction to reflect *anticipation* of impending punishment, while they do develop a normal SCR to the gain or loss experienced as a *consequence* of their choice (Bechara, Tranel, Damasio, & Damasio, 1996).

AMG lesion patients, like the OFC lesion patients, also experience reduced SCRs during the IGT; however, AMG lesion patients did not produce a change in SCR either before a decision *or* in response to gain or loss feedback (Bechara et al., 1999). Without the ability to effectively process the emotional aspects of feedback in the IGT, lesion patients, as well as many other neurological and psychiatric patient populations, perform poorly. Classical IGT results from patients with AMG and VMPFC lesions by Bechara, et al. (1999) are illustrated in **Figure II-2**.

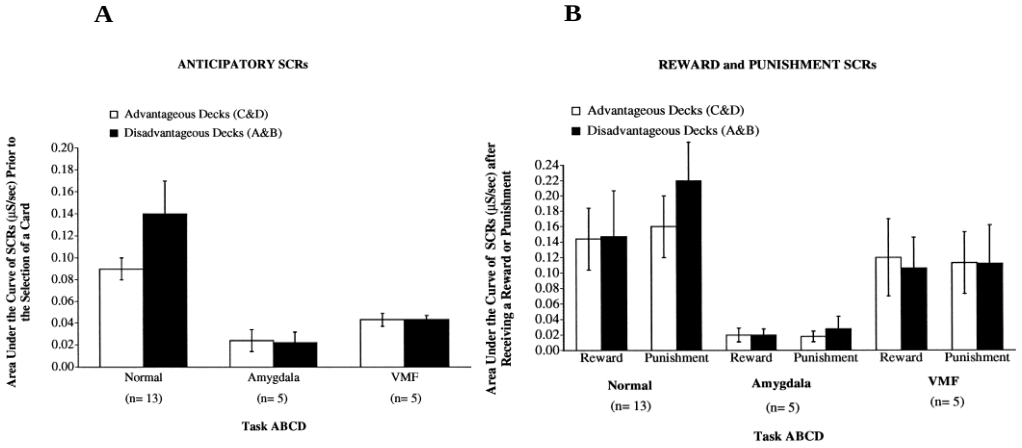

Figure II-2. *Anticipatory skin conductance responses (SCRs) (A) and reward/punishment SCRs (B) (μS/sec), generated by normal controls, patients with amygdala lesions, or patients with ventromedial frontal lobe (VMF) lesions as a function of choice in the Iowa Gambling Task.* Error bars indicate standard errors (Bechara et al., 1999).

In general, in contrast to emotional functions, the impact of executive functions on IGT performance is seen as rather minimal, and many neuropsychological patient studies found no correlations between IGT and tests of executive functions (see also reviews by Dunn et al., 2006a; Gleichgerrcht, Ibanez, Roca, Torralva, & Manes, 2010). However, while early task blocks (usually blocks 1 and 2; trials 20-40) may test true decision making under ambiguity, the later task blocks (blocks 3-5; trials 60-100) also assess decision making under risk. Thus, once contingencies between choices and feedback have been learned, the task is no longer just implicit, but risks associated with choosing each deck become, in principle, calculable. Thus, executive functions can also play a role in the IGT (Brand, Grabenhorst, Starcke, Vandekerckhove, &

Markowitsch, 2007; Brand, Recknor, et al., 2007; Hinson, Jameson, & Whitney, 2002; Jameson, Hinson, & Whitney, 2004), but they do so mostly in the final task blocks (Brand et al., 2006). A recent study tested whether the IGT had convergent validity with tests of executive functions and if so, in what phase of the task (Gansler, Jerram, Vannorsdall, & Schretlen, 2011). While IGT involved attentional and novel problem solving abilities throughout the entire task more so than executive function, a stronger relationship between IGT and executive functions was observed when IGT trials after the first 40 trials were analysed. Finally, performance in the final trials of the IGT, as opposed to earlier trials, was more strongly correlated with performance in the Game of Dice Task (GDT), a task that measures decision making under risk (Brand, Recknor, et al., 2007). The GDT has been more consistently related to executive functions than the IGT and is the primary measure of interest in the current study.

2.1.2. Decisions under risk: Game of Dice Task (GDT)

The Game of Dice Task (GDT; Brand et al., 2002) is a computerized gambling task that assesses decision making under risk. The GDT provides explicit and stable probabilities regarding gains and losses. Therefore, unlike the IGT, in the GDT there is no requirement for the individual to implicitly detect and learn response contingencies. The goal of the GDT is to win as much money and to lose as little money as possible by predicting the outcome of a single, randomly-thrown die (see **Figure II-3**).

Figure II-3. *Illustration of the Game of Dice Task* (Brand et al., 2002).

An individual begins the task with a game money balance of $1000. In a total of 18 rounds, they may choose to select a single number or a combination of two, three, or four numbers to bet on the outcome of a single die throw. The single die is thrown in each trial may match the bet the individual made. For example, if the individual bets on the combination of numbers 1, 2, and 3, and the subsequently die thrown equals '3', the individual would win $200. If the die thrown equals '4', the individual would lose $200. As illustrated in **Figure II-3**, the bets vary in their risk level and their associated fictitious wins or losses (1-number bets: 1:6 chance of winning $1000, and a 5:6 chance of losing $1000; 2-number bets: 2:6 chance of winning $500, and a 4:6 chance of losing $500; 3-number bets: 3:6 chance of winning $200, and a 3:6 chance of losing $200; 4-number bets: 4:6 chance of winning $100, and a 2:6 chance of losing $100). Thus, choices with a lower probability of winning (i.e., risky choices) are associated with potentially larger wins, as well as larger losses, whereas choices with a higher probability of winning (i.e., non-risky choices) are associated with smaller wins, as well as smaller losses. Importantly, the GDT overtly shows these contingencies throughout the entire task.

After each trial, visual and auditory feedback is provided regarding the outcome of the subject's selection. Visual feedback involves the following being displayed on the screen: the die number that was thrown, the amount of money

won or lost (depending on whether or not the actual thrown die number is congruent with the selection made), the adjustment of the running balance, and a colored bar graph symbolically representing the change in capital. Auditory feedback is given after each trial outcome and consists of a cash-register-like sound for a win and a penalty-like sound for a loss in that trial. Participants complete the 18 trials of the GDT in approximately 5-10 minutes. The most common outcome measure of the GDT is a total net-score. In detail, safe or advantageous choices in the GDT are three- or four-number combinations, since their associated probability of winning is more or equal to 50%. Risky or disadvantageous choices in the GDT are single numbers or two-number combinations, since their associated probability of winning is less than 50%. The GDT net-score is created by subtracting the number of risky decisions from the number of safe decisions (the net-score has a maximum of 18 and a minimum of -18). Therefore, a higher net-score indicates better decision making performance in the GDT.

To date, the GDT has been used most often to study adult clinical samples, for example Korsakoff Syndrome (Brand, Fujiwara, et al., 2005), pathological gambling (Brand, Kalbe, et al., 2005), Parkinson's disease (Brand, Labudda, et al., 2004), Alzheimer's disease (Delazer, Sinz, Zamarian, & Benke, 2007), bulimia nervosa (Brand, Franke-Sievert, et al., 2007), and binge eating disorder (Svaldi, Brand, & Tuschen-Caffier, 2010). The GDT detected impairment in all of those populations. The GDT has also been used in studies with healthy participants (e.g., Brand, 2008; Brand, Heinze, Labudda, & Markowitsch, 2008; Brand, Laier, Pawlikowski, & Markowitsch, 2009) to investigate involvement of cognitive and emotional aspects and the behavioral conditions that the GDT and decisions under risk operate with. In both clinical studies and studies in healthy controls, it has been found that performance on the GDT is strongly associated with executive functions. As such, Brand et al. (2005; 2006; 2007; 2008) showed across different patient populations that GDT performance was consistently correlated with performance in the Modified Card Sorting Test (MCST; Nelson,

1976) or the WCST (Bagneux, Bollon, & Dantzer, 2012; Brand, Fujiwara, et al., 2005; Brand, Kalbe, et al., 2005). Additionally, a study by Brand and colleagues (2009) investigated the potential role of other cognitive functions, for example intelligence and calculative strategies (i.e., strategies that involve calculating winning probabilities), in moderating GDT performance. Data showed that participants with high intellectual abilities as well as those who use calculative decision strategies performed better in the GDT, independent of whether they received feedback for their choices. By contrast, individuals with lower intelligence and those who used non-calculative (intuitive) decision strategies performed worse in the GDT when they did not receive feedback than in situations when feedback was provided. That is, even though it is not essential to perform the task, the feedback component of the GDT shapes decisions but it does more so in individuals who do not have a high capacity to calculate probabilities.

As described above, while the VMPFC/OFC is more closely associated with feedback and reward/emotional processing (e.g., Bolla, Eldreth, Matochik, & Cadet, 2005; Kringelbach & Rolls, 2004; Rolls, 2000, 2004; Thiel et al., 2003), the DLPFC is a key region mediating executive functions involved in decision making (e.g., evaluating decision options, predicting future outcomes and probabilities, developing and maintaining decision goals; for a detailed review, see (Mansouri, Tanaka, & Buckley, 2009). As such, the DLPFC is important for categorizing alternatives regarding their risk and strategic aspects of decision making (e.g., goal definition in the long term), especially when the environment is stable, such as in the case of the GDT (e.g., Brand, Kalbe, et al., 2004; Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006; Lie et al., 2006; Newman, Carpenter, Varma, & Just, 2003). Additionally, guiding attentional processes of behavioral relevance (Buckley et al., 2009; Kennerley & Walton, 2011; Mansouri, Buckley, & Tanaka, 2007) based on the representation of reward value (Kim, Hwang, & Lee, 2008; Roesch & Olson, 2003) in order to prioritize consequential information and streamline decision making also requires the DLPFC.

Furthermore, patients with Parkinson's disease (PD) are often used as a model of decision making deficits resulting from disruptions in fronto-striatal communication. Of note, connections between the DLPFC and the striatum (the "dorsolateral prefrontal-striatal loop") are affected early in the course of PD, while the limbic-orbitofrontal-striatal loop seems to be spared early on (Owen, 2004). In this context, Euteneuer et al.'s (2009) results are particularly interesting. In this study they assessed PD patients without dementia and healthy controls on both, the IGT and the GDT. Patients with PD were significantly impaired on the GDT but not the IGT. Furthermore, impairments in executive functions correlated positively with performance on the GDT only, and not the IGT. In light of these results, DLPFC dysfunction in earlier stage PD patients without dementia was assumed to underlie deficits in decision making under explicit rules (see also another study finding GDT impairments related to executive functions in PD patients (Brand, Labudda, et al., 2004). A complementary study by Labudda and others (2009) illustrates a possible double dissociation by finding medial temporal lobe epilepsy patients (i.e., with damage or dysfunction in the hippocampus and/or AMG) to be impaired in the IGT but not the GDT.

2.1.3. Similarities between IGT and GDT

Despite stronger associations between executive functions and decision making in the GDT compared to decision making in the IGT, the tasks share a similar feedback component. As outlined above, both tasks require perception, processing, and integration of reward/punishment signals. Not surprisingly then, a significant negative correlation between the number of risky decisions in the GDT and the frequency of using negative feedback following a risky decision (in order to shift to a non-risky decision in the next trial) was revealed (such as in patients with pathological gambling (Brand, Kalbe, et al., 2005) or with Parkinson's disease (Brand, Labudda, et al., 2004). The additional benefit of feedback processing in GDT performance is also evident in healthy populations. In a study by Brand, et al. (2008), healthy participants were administered both the original version of the GDT as well as a version of the GDT without feedback (i.e., the

outcome of the die was not revealed nor was any indication of a win or loss) and a brief neuropsychological battery to explore the importance of feedback in successful GDT performance. Results indicated that healthy participants performed well on both versions of the GDT (as indicated by positive net-scores); however, participants performed more advantageously in the original GDT with feedback than in the modified GDT without feedback. Although these results emphasize the role of feedback in the GDT, one has to keep in mind that the healthy participants were nevertheless able to perform advantageously without feedback. This implies that the information offered in the GDT from the outset of the task (amounts of gains, losses and their probabilities) is, in principle, sufficient to perform advantageously during the entire task, even without any trial-by-trial feedback. In both versions of the GDT, decision making correlated with executive functioning (Brand et al., 2008).

Further evidence that feedback in the GDT causes an emotional response comes from a study by Brand, Grabenhorst, Starcke, Vandekerckhove & Markowitsch (2007) that involved three patients with damage to the AMG (in the course of Urbach-Wiethe disease, a rare recessive genetic, primarily dermatological condition that also leads to relatively selective calcifications of the bilateral amygdala [Staut & Naidich, 1998]) who were administered both the IGT and the GDT to investigate the nature of their decision making deficits. In this study, all three patients with Urbach-Wiethe disease had deficits in the IGT *and* in the GDT. Patients with additional executive dysfunctions were particularly impaired in the GDT. Patients also showed lower anticipatory and feedback-related SCRs in both the IGT and GDT. Thus, deciding advantageously under risk in the GDT involves both the use of feedback from previous trials, similar to the IGT decisions under ambiguity, and in addition, executive functions. Finally, Wilbertz and others (2012) found in an fMRI study that patients with attention deficit hyperactivity disorder showed reduced VMPFC activity while processing (high or low) monetary reward cues. Patients were also impaired in the GDT administered outside the scanner. Most importantly, their VMPFC activity

reductions during the reward processing task were inversely related to GDT performance. These results underscore the importance of reward processing and the feedback component in the GDT.

Taken together, results indicate that the GDT strongly relies on executive functions and, although less pronounced than in the IGT, on the processing of emotional decision feedback (Brand, 2008).

2.2. Decision making in MS

There are no previous studies in MS patients with the GDT, and most studies have used the IGT. One recent study by Simioni et al. (2012) has used two experimental tasks measuring decision making under risk, the Wheel of Fortune Task (WOF; Camille et al., 2004) and the Cambridge Gambling Task (CGT; Rogers et al., 1999). **Table II-1** gives a summary of previous studies of decision making in MS. Each of these studies is described in more detail following the table.

Table II-1. *Summary of prior decision making studies in MS patients*

Study	Participants	Task	EDSS	Disease Duration	Patients' decision making impairment	Correlation with EF	Correlation with other behavioural variables	Correlation with peripheral/brain variables
Kleeberg et al. (2004)	16 RRMS, 4 SPMS, 16 HC	IGT	Med. 2.0 (1.5-6.5)	Med. 8.58 yrs. (7 mth-25 yrs)	IGT learning slope, especially in patients with EDSS > 2.	None	IGT learning slope was associated with education, EDSS, disease duration, anxiety, DEX, TMT-A	IGT learning slope was associated with reduced SCRs in patients
Nagy et al. (2006)	21 RRMS 30 HC	IGT; two versions	1.7 (0-3)	M: 3.1 yrs ± 1.1 yrs	IGT net-score in both task versions	None	No correlations with BADS	None assessed
Roca et al. (2008)	12 RRMS, 12 HC	IGT	0-1.5	M: 2.46 yrs (11 mth.-3 yrs)	IGT net-score only in the last task block	None	None assessed	IGT net-score was uncorrelated with brain white matter integrity (DTI)
Simioni et al. (2008)	109 RRMS, 56 CIS, 50 HC	IGT	1.74 (0-2.5)	M: 2.1 yrs (3 mth.-5 yrs)	IGT learning index slightly more impaired in patients with a recent MS relapse than in those without relapse	None	IGT learning index was associated with education, depression. In patients without MS relapse: IGT learning slope was correlated with DEX and personality change	None assessed
Simioni et al. (2009)	68 RRMS, 2 SPMS, 50 HC (subset of Simioni et al.; 2008)	IGT	Med. 2.0 (1.5- 3.5)	Med. 4 yrs (2.4- 8.5 yrs.)	Follow-up to Simioni et al. (2008) without direct comparison to controls at time 2; IGT learning index decreased over time	None	Decrease in IGT learning index was correlated with quality of life, emotional well-being and IGT score at baseline (in Simioni et al., 2008)	None assessed
Simioni et al. (2012)	72 RRMS 38 HC	CGT WOF	1.9 (1.5-3.5)	M: 5.06 yrs ± 3.3 yrs	WOF: less use of positive counterfactual information; more risk aversion; less reported negative emotions. CGT: Decision quality and deliberation time; no change in overall gains	None	CGT deliberation time was associated with PASAT 3"	Patients' post-decisional SCRs in WOF were not different from those of the controls

CGT: Cambridge Gambling Task; CIS: clinically isolated syndrome; DEX: Dysexecutive Questionnaire; EDSS: Expanded Disability Status Scale; EF: Executive functions; HC: healthy controls; IGT: Iowa Gambling Task; M.: Mean; Med.: median; mth.: months; PASAT 3": Paced Auditory Serial Additions Test, 3 second version; RRMS: relapsing-remitting multiple sclerosis; SCR: skin conductance response; SPMS: secondary progressive multiple sclerosis; TMT-A: Trail Making Test- version A; WOF: Wheel of Fortune Task; yrs, years

2.2.1. Kleeberg, Bruggimann, Annoni, van Melle, Bogousslavsky and Schluep (2004)

Kleeberg and others (2004) were the first to assess decision making in MS, using the IGT. While administering the IGT, patients' SCRs were recorded during the 5-second interval before selecting a card from a deck and during the 5-second interval when the outcome of the choice was displayed. Overall, the number of disadvantageous choices was not significantly higher in the MS patient group than in the comparison group, but the difference in learning slopes differed between groups (the comparison group learned to prefer the advantageous decks over the course of the IGT more quickly as compared to MS patients). In the final blocks of the task especially, patients demonstrated more impairment than the comparison group. MS patients were further subdivided based on disability (EDSS scores either smaller/equal to or larger than 2.0). Compared to controls, impairment in the learning process was more pronounced in MS patients with a higher EDSS score (> 2.0) and in those with longer disease duration. The temporal evolution of MS patients' choices showed that patients with an EDSS score greater than 2.0 demonstrated a delay in learning to avoid disadvantageous choices, whereas the lower EDSS score subgroup showed an inconsistent learning pattern characterized by an early, but non-systematic, decrease in disadvantageous choices. Interestingly, these two types of learning impairments in decision making were also associated with different patterns of emotional responsivity, as shown by the recorded SCRs throughout the IGT. The comparison group had an increase in amplitude for anticipatory SCRs preceding disadvantageous decks and an increase in SCRs following punishment as compared to patients. The SCRs in the patients with higher EDSS scores/longer disease duration were not only of smaller amplitude than those in the comparison group, but they also did not increase throughout the IGT, suggesting an inability to develop sufficient autonomic arousal in this task. Interestingly, patients with higher self-reported anxiety scores in the Hospital and Anxiety Depression Scale (HADS) learned faster than less anxious patients. The group with higher DEX self-rating scores (i.e., a higher self-report score for dysexecutive symptoms such as, "I act without thinking, doing the

first thing that comes to mind" or "I have difficulty thinking ahead or planning for the future") showed significantly slower learning. There was no significant decrease in the number of disadvantageous choices made over time when comparing the groups with low and high scores in the BADS, indicating that objective measures of executive functions were not related to IGT performance. In summary, Kleeberg, et al.'s results demonstrated that IGT decision making can be impaired in MS, particularly in patients with a higher EDSS score. Although cognitive variables (i.e., BADS) did not seem to influence IGT performance strongly, self-reported neuropsychiatric symptoms as well as emotional reactivity (i.e., anxiety, DEX, SCRs) were associated with impaired learning in the IGT.

2.2.2. Nagy, Bencsik, Rajda, Benedek, Beniczky, Kéri, et al. (2006)

In this study, two versions of the IGT (classic and modified) and a standard neuropsychological battery (Lezak, 1995), including the WCST (Berg, E. A., 1948; Grant & Berg, 1948), Digit Spans (Wechsler, 1997), the SDMT (Smith, A., 1982) and Verbal Fluency (Borkowski, Benton, & Spreen, 1967), was administered to MS patients and controls. The classic version of the IGT has initial high gains for decks A and B (i.e., those two decks that lead to even larger losses later on, and are therefore disadvantageous) that investigate sensitivity to reward. That is, individuals are lured into a risky choice by large immediate gains even though there will be even larger future losses. The second IGT version was modified so that decision making dysfunctions are a result of the failure of high rewards to outweigh immediate punishments. In this version, advantageous decks are characterized by high immediate loss but higher future reward. If decision making dysfunctions are due to insensitivity to any long-term outcomes, regardless whether reward- or punishment-based, patients will show impairments in both versions of the IGT (Bechara et al., 2000). In this study, MS patients' decision making was impaired in both versions of the IGT. In both versions of the IGT, as the task progressed, patients' decision making impairments became increasingly apparent. The difference between patients and controls were most prominent in the later task blocks and could suggest a failure to develop a

consistent decision strategy and executive deficits. However, none of the cognitive tests, including tests of executive functions, predicted performance in either IGT version. Since patients were impaired in both IGT versions, the authors concluded that insensitivity to any long-term decision outcomes, and not necessarily rewards, contributed to MS patients' impaired decision making. These results here suggest that even relatively early-stage MS patients (EDSS: 0-3; disease duration: 3.1 yrs ± 1.1 yrs) can have impaired IGT performance, however, they seem to be unrelated to other cognitive functions.

2.2.3. Roca, Torralva, Meli, Fiol, Calcagno, Carpintiero, et al. (2008)

This study assessed IGT decision making and other executive and cognitive functions along with diffusion tensor imaging (DTI) in a small group of 12 patients with early RRMS and mild disability (EDSS < 2) and healthy controls. DTI is used to reveal abnormalities in WM fiber structure and to provide models of brain WM connectivity (Hagmann et al., 2006). The standard cognitive battery in this study included many tests that largely assessed language and vocabulary, praxis, memory, executive functions, and general intelligence. Importantly, in addition to measuring executive functions with more traditional tests (WCST, TMT, Digit Span, Letters and Numbers subtest of the WAIS), a specific executive function battery consisting of tests that are more closely related to activities of daily life (and have proven to be sensitive to detect prefrontal cortex dysfunction) was also given (the PASAT; Gronwall, D. M., 1977), the Faux Pas Test (Thornton, Raz, & Tucke, 2002), the Reading the Mind in the Eyes Test (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997), the Hotel Task (Manly, Hawkins, Evans, Woldt, & Robertson, 2002), and the Multiple Errands Test (Knight, Alderman, & Burgess, 2002). The MS patients showed impairment in memory and in some of the tasks from the specific executive function battery, but not in classical executive tests. There were also slight differences between the two groups in the IGT, but these were confined to the final task block. Although MS patients displayed significant differences in some frontal white fiber bundles compared to controls, IGT performance did not correlate with these DTI

measures. Frontal WM changes did correlate with performance on some of the other tasks (the PASAT, Multiple Errands Test and one subtask of the Hotel Task), but none of the classical executive functions tests (e.g., the WCST). In summary, MS patients were impaired in the last IGT task blocks, but these deficits were neither related to any of the conventional neuropsychological tests nor to neurological markers showing fronto-subcortical dysfunction.

2.2.4. Simioni, Ruffieux, Kleeberg, Bruggimann, Annoni, & Schluep (2008)

To test whether impairment in decision making may serve as an early marker of cognitive-emotional deterioration in CIS/MS, Simioni, Ruffieux, Kleeberg, Bruggimann, Annoni, & Schluep (2008) investigated decision making impairment in a large sample of early-stage patients, including patients with CIS, see **Table II-1** for details. In addition to the IGT, the Rey Auditory Verbal Learning Test (Rey, 1941), the BADS and the TMT were administered. The investigators also assessed neuropsychiatric symptoms with the DEX, Iowa Scale of Personality Change (ISPC; Barrash, Anderson, Jones, Wefel, & Tranel, 1997), the Fatigue Assessment Instrument (FAI; Schwartz, Jandorf, & Krupp, 1993), HADS, London Handicap Scale (LHS; Harwood, Gompertz, & Ebrahim, 1994), the French version of the Multiple Sclerosis Quality of Life Questionnaire (SEP-59; Vernay et al., 2000), and a semi-structured psychiatric interview using DSM-IV criteria in patients. While the IGT net-score was numerically greater in the control group than in the patient group, the difference was far from being statistically significant. Additionally, when the patient subgroups (definite MS and CIS) were separately compared with controls, IGT net-score was still not statistically significant between each subgroup and the controls. Patients' IGT performances during the final blocks of the IGT as well as their IGT "learning index" (calculated by subtracting the averaged net-score across the first two from the last three IGT blocks) were not different from controls. MS patients who experienced a relapse during the 15 months following their inclusion in the study and patients who did not experience a relapse (i.e., stable patients) were then examined. While the IGT net-score was not significantly different, relapsing

patients had a worse IGT learning index than stable patients. The IGT learning index was positively influenced by the educational level but negatively influenced by the co-occurrence of minor depression. None of the various measures of the IGT employed were correlated with any parameter of psychosocial or cognitive functioning. This study demonstrated that decision making is generally preserved in prodromal or early-stage MS patients compared to controls, but that low education, depression and disease relapses may have a detrimental effect on decision making even in early disease stages.

2.2.5. Simioni, Ruffieux, Kleeberg, Bruggimann, Du Pasquier, Annoni and Schleup (2009)

This was a longitudinal follow-up study on part of the sample from their Simioni et al. (2008) study. Retesting with a parallel version of the IGT took place after a minimal period of 2 years dated from baseline assessment and only with patients who had confirmed MS. Results showed that IGT performances in patients decreased over time, instead of improving with repeat exposure to the task. MS patients with deficits in the IGT were more likely to show a poorer perceived health status and emotional well-being; however, longitudinal IGT performance was not associated with more relapses and disability progression over the follow-up time and occurred independently of MS course and disease evolution. As with Simioni et al. (2008) study, IGT performance was not related to any other cognitive measures. The initial IGT score itself was the only predictor of follow-up IGT performance. The results of this study could not relate dysfunction in the IGT to executive deficits or to general cognitive impairment. In conclusion, in Simioni et al.'s studies, an emerging decline in IGT decision making abilities presented as an isolated deficit, even though it was apparent in the still relatively mildly disabled group of MS patients in their follow-up study in 2009.

2.2.6. Simioni, S., Schluep, M., Bault, N., Coricelli, G., Kleeberg, J., Du Pasquier, R. A., Gschwind, M., Vuilleumier, P. & Annoni, J. M. (2012)

Finally, an interesting recent study by Simioni and colleagues (2012) assessed decision making under risk using two experimental tasks in a sample of 70 RRMS patients. Since neither of these tasks has been described in this thesis so far, they are briefly outlined here. Both tasks are assumed to measure decision making under risk, since outcome probabilities and amounts of to-be-won or lost fictitious money or points are explicitly shown to the participant.

A) The Wheel of Fortune Task (WOF; Camille et al., 2004) measures emotional reactions underlying decision making under risk. For healthy controls, the WOF's advantageous decisions can be induced through prior experience of disappointment and regret (Camille et al., 2004). In this computerized task, participants are shown two wheels, each divided into two sectors associated with explicit amounts of money (e.g.,-50$, +50$, -200$, +200$) and different outcome probabilities (0.8, 0.2, and 0.5). Participants are asked to select one of the two wheels, and within each a spinner then selects one of the two sectors. Feedback about money won or lost is then provided and subsequently, participants rate their feelings on a scale from very negative to very positive. In a "partial feedback" condition, the spinning arrow and the related outcome are only displayed for the selected wheel. Thus, the obtained outcome (if negative) can trigger *disappointment* when compared with a potentially more favorable (but not known) outcome. In contrast, in a "complete feedback" condition, outcomes are shown for both the selected and the non-selected wheels. These trials are thought to induce not only disappointment but also *regret* by showing the outcome that could have been obtained if participants had selected the other wheel (for example, when a participant lost $200 and is shown that choosing another wheel could have resulted in a win of $200). Thus, the WOF measures the impact of so-called counterfactual thinking (the mechanism that allows one to compare "what is" with "what might have been") on the decision process. Healthy individuals usually report emotional responses consistent with counterfactual thinking by

choosing to minimize future regret and learning from their emotional experience by becoming more risk averse over the course of the task. Patients with OFC lesions do not report regret or learn to anticipate negative consequences of their choices based on prior outcomes and emotional reactions (Camille et al., 2004). Dependent variables in the WOF are the use of counterfactual information to adjust future decisions, development of risk aversion over trials, and the reported post-decisional emotions (disappointment, regret). Of note, elements of this task are embedded into the GDT insofar as it provides only complete feedback by showing the result of the thrown die (counter one's own choice) explicitly in each trial.

B) The Cambridge Gambling Task (CGT; Rogers et al., 1999) is a computerized task where participants are presented with a row of ten red or blue boxes and are asked to bet on whether a token has been hidden under a red or a blue box. The proportion of boxes of each color changes in each trial. Healthy participants are expected to adjust their bet according to the relative proportion of red to blue boxes by betting on the correct colour and by betting fewer points if the odds of winning are lower (i.e., the winning probability is higher for betting on red boxes when more red than blue boxes are present). Of note, the task terminates if the participant runs out of points to bet and premature termination is the strongest indicator for dysfunctional decision making under risk in the CGT. Dependent variables in the CGT are trial number to termination and overall gains, decision quality (betting on the higher probability colour and adjusting the number of points betted) and decision deliberation time. Unlike in the GDT, participants do not need to generate long-term decision strategies in the CGT because decisions are based on winning probabilities associated with the specific box ratio in each trial. Similar to the GDT, winning probabilities and point/account balance are displayed explicitly throughout the task.

In Simioni et al. (2012), RRMS patients showed differences in both decision making tasks compared to controls. In the WOF, analyzing trial-by-trial contingencies between condition, choice, outcome and associated reported

emotion, the authors tested whether participants developed a preference for making risky or cautious decisions, made use of counterfactual information (in the complete feedback condition), and whether current negative emotions (disappointment in partial feedback trials and regret in complete feedback trials) influenced further decision making. Patients showed less use of positive counterfactual information and more risk aversion than controls. They also reported less negative emotions during the task than controls (both disappointment in partial feedback trials and regret in complete feedback trials). However, SCRs assessed during the WOF did not show significant post-decisional differences between patients and controls. In the CGT, the quality of patients' decisions (i.e., making adjustments to their decisions based on the displayed probabilities) was lowered and they deliberated longer to make decisions. Their overall number of trials played in the CGT before running out of points to bet was not lowered. Apart from a correlation between CGT deliberation time and attention/ information processing speed in the PASAT, none of the cognitive measures, including executive functions tests, were associated with performance in either of the two decision making tasks.

2.2.7. Decision making in MS: summary and integration

Of note, the majority of the above-mentioned studies used the IGT to assess decision making, but had different ways of reporting IGT performance, ranging from net-score (total or per IGT task block), learning index, learning slope, total errors. These inconsistencies make it difficult to compare and synthesize the results across multiple studies. Despite this, in summarizing all of the above IGT studies, deficits are present but seem minimal in MS (Kleeberg et al., 2004; Nagy et al., 2006; Roca et al., 2008; Simioni et al., 2009). Although these decision making deficits can occur in MS patients with relatively short disease duration and mild neurological impairment (Nagy et al., 2006; Roca et al., 2008) (but see Simioni et al., 2008), they become more pronounced in MS patients with higher disability (i.e., higher EDSS scores, disease duration, progressive MS subtype) (Kleeberg et al., 2004). Impairment in the IGT was

rather independent of other measures of neurological, cognitive or structural brain changes associated with the disease, but was sometimes correlated with behavioural or emotional changes (e.g., physiological responses to reward/punishment in form of SCRs; anxiety; self-reported dysexecutive functions [Kleeberg et al., 2004; Simioni et al., 2008]). Roca and others (2008) were the only study to incorporate brain imaging (DTI), but found IGT performance unrelated to fronto-subcortical WM integrity in MS patients. Although executive functions were assessed in all studies, none of them found correlations to any of the IGT performance measures. Impairments in decision making under risk in MS has only been tested in one study, showing changes in RRMS patients compared to controls (Simioni et al., 2012). The use of two experimental tasks here indicated slight modifications of decision making under risk in MS. In both tasks, patients were less able to select optimal choices based on explicit outcome probabilities, showed changes in overt emotional experiences associated with their choices, but had no changes in (covert) physiological responses. Overall, differences between patients and controls in the two tasks did not indicate global deterioration of decision making under risk, but slight alterations based on dysfunctional use of emotional information from trial-to-trial or mental slowing.

Taken together, MS-associated changes in emotional processing, but not cognitive dysfunctions dominated prior findings of decision making deficits in MS. The findings were derived almost exclusively with decision making tasks designed to assess primarily emotional aspects of decision making. The one study using the CGT, a task that comes closest to the GDT in assessing a more cognitive type of decision making, found an association with processing speed, although not with executive functions. Two studies pointed to more pronounced deficits in later IGT blocks in MS patients (Nagy et al., 2006; Roca et al., 2008), and this may imply that MS patients are more impaired in decision making tasks relying more definitively on executive functions, such as the GDT. Brain substrates of potential decision making deficits in MS are largely unknown with only one study assessing WM integrity and finding no association with IGT deficits.

2.3. Decision making in neurodegenerative conditions

As outlined in **Section II-1.6.1**, MS is increasingly associated with both cortical and subcortical neurodegenerative processes (Batista et al., 2012; Benedict et al., 2013; Benedict et al., 2009; Bermel et al., 2003; Calabrese, M., Mattisi, et al., 2010; Cifelli et al., 2002; Gilmore et al., 2006; Houtchens et al., 2007; Prinster et al., 2006; Sepulcre et al., 2006; Vercellino et al., 2005) and these might even be of primary nature (Bakshi, Dmochowski, Shaikh, & Jacobs, 2001; De Stefano et al., 2003; Fisher et al., 2008; Horakova et al., 2009; Pirko, Lucchinetti, Sriram, & Bakshi, 2007; Sanfilipo, Benedict, Weinstock-Guttman, & Bakshi, 2006; Vercellino et al., 2005). Neurodegenerative processes, especially GM atrophy, have a strong relationship to cognitive impairment in MS. Therefore, the following section briefly reviews existing evidence on decision making deficits in primary neurodegenerative conditions. A recent review article by Gleichgerrcht et al. (2010) was taken as the basis of this review, and complemented by more recent studies.

Decision making both under ambiguity and risk has been investigated in a variety of neurodegenerative populations. Depending on the condition, a particular pattern of neuropathological changes that lead to brain tissue loss can be anticipated. For example, degeneration in cortical brain areas is commonly found in frontotemporal dementia (FTD; superior medial and orbito-frontal lobes [Seltman & Matthews, 2012]) and Alzheimer's disease (AD; medial and lateral temporal lobes, frontal and parietal cortices [Wenk, 2003] and basal forebrain [Schliebs, 2005]), whereas subcortical degeneration is more characteristic of Parkinson's disease (PD; loss of dopaminergic neurons in the substantia nigra/basal ganglia [Jankovic, 2005]) and Huntington's disease (HD; loss of spiny projection neurons in the neostriatum [Albin, Young, & Penney, 1989]). **Table II-2** provides a summary of decision making performance in FTD, AD, PD and HD samples, using the IGT and GDT, and the neuroanatomical correlates associated with decision making task performance.

Table II-2. *Summary of main findings from IGT and GDT studies in patients with neurodegenerative disorders* (see Gleichgerrcht et al., 2010).

Decision making paradigm: IGT

Neurodegenerative Disease	Study	Participants	Patients' decision making impairment	Correlations with EF	Correlations with other behavioral variables	Correlations with peripheral/brain variables
Frontotemporal Dementia (FTD)	Torralva et al. (2007)	20 FTD, 10 HC	IGT: Yes	No correlations	No correlations	No correlations
	Torralva et al. (2009)	35 FTD, 14 HC	IGT: Yes	Yes: impaired mental flexibility on WCST	No correlations	None assessed
	Manes et al. (2010)	1 FTD	IGT: Yes	No correlations	No correlations	Yes: MRI frontal lobe atrophy
	Bertoux et al. (2012)	20 FTD 20 AD 30 Old HC 16 Young HC	IGT: No	None assessed	No correlations	None assessed
	Poletti et al. (2013)	10 FTD	IGT: Yes	Yes: FBI for negative symptoms	Yes: Mind in the Eyes Test	None assessed
Alzheimer's Disease (AD)	Torralva et al. (2000)	25 AD, 20 HC	IGT: Yes	No correlations	Yes: impaired memory	None assessed
	Sinz et al. (2008)	22 AD, 22 HC	IGT: Yes	Yes: deficient inhibitory control subtest in FAB	No correlations	None assessed
	Bertoux et al. (2012)	20 FTD 20 AD 46 HC	IGT: No	None assessed	No correlations	None assessed
Parkinson's Disease (PD)	Stout et al. (2001)	14 HD, 22 PD, 42 HC	IGT: HD more impaired than PD	No correlations	Yes: In the HD groups, MDRS conceptualization and memory	None assessed
	Czernecki et al. (2002)	23 PD, 28 HC	IGT: No	Yes: commission and omission scores in a stimulus-reward learning task	Yes: age and education	None assessed
	Thiel et al. (2003)	5 PD, 5 HC	IGT: No	No correlations	No correlations	Yes: decreased activity in fronto-subcortical loops
	Perretta et al. (2005)	16 early PD, 16 late PD, 19 HC	IGT: Yes	No correlations	Yes: BDI total score in early PD	None assessed
	Mimura et al. (2006)	18 PD, 40 HC	IGT: Yes	No correlations	Yes: affective component of ToM	None assessed
	Pagonabarraga et al. (2007)	35 PD, 31 HC	IGT: Yes	No correlations	Yes: inverse with memory and GCP	None assessed
	Kobayakawa et al. (2008)	34 PD, 22 HC	IGT: Yes	No correlations	Yes: the SDS score	Yes: decreased SCRs
	Ibarretxe-Bilbao et al. (2009)	24 early PD, 24 HC	IGT: Yes	No correlations	Yes: Ekman emotional face recognition and RDS	Yes: GM loss in the right amygdala and in the OFC
	Euteneuer et al. (2009)	21 PD, 23 HC	IGT; GDT: Yes in GDT	Yes: MCST and FAS with GDT	No correlations	Yes: impaired EDRs
	Delazer et al. (2007)	20 PD, 19 PDD, 20 HC	IGT: Yes in PD and PDD patients	Yes: TMT-A and B	No correlations	None assessed
	Poletti et al. (2010)	30 PD, 25 HC	IGT: No	No correlations	Yes: BIS-11 Self Control subscale	None assessed

Decision making paradigm: GDT

Neurodegenerative Disease	Study	Participants	Patients' decision making impairment	Correlations with EF	Correlations with other behavioral variables	Correlations with peripheral/brain variables
Alzheimer's Disease (AD)	Delazer et al. (2007)	19 AD, 25 HC	GDT: No	Yes: TMT-A and B	Yes: age	None assessed
Parkinson's Disease (PD)	Brand et al. (2004)	20 PD, 20 HC	GDT: No	Yes: impaired mental flexibility and set-shifting on MCST	No correlations	None assessed
	Euteneuer et al. (2009)	21 PD, 23 HC	GDT; IGT: Yes in GDT	Yes: impaired MCST and FAS with GDT	No correlations	Yes: impaired EDRs
	Labudda et al. (2010)	10 PD, 12 HC	GDT (behavioral and fMRI version): Yes in behavioral	None assessed	None assessed	Yes: fMRI indicated reduced parietal activation in patients
	Rossi et al. (2010)	7 PD with PG, 13 PD	IGT, GDT: Yes in IGT; Patients with PG more impaired	No correlations	No correlations	None assessed

AD, Alzheimer disease; BDI, Beck Depression Inventory; BIS-11, Barratt Impulsiveness Scale; CGT, Cambridge Gambling Task; DBS-STN, deep brain stimulation of the subthalamic nucleus; EDRs, electrodermal responses; EMG, electromyography; EF, executive functions; FAB, Frontal Assessment Battery; FAS, Controlled Oral Word Association Test; FBI, Frontal Behavior Inventory; FTD, frontotemporal dementia; GDT, Game of Dice Task; GCP, global cognitive performance; HC, healthy controls; HD, Huntington disease; IGT, Iowa Gambling Task; MDRS, Mattis Dementia Rating Scale; MCST, Modified Card Sorting Test; OFC, orbitofrontal cortex; PG, pathological gambling; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; RDS, reverse digit span; SDS, Zung's self-rating depression scale; SCR, skin conductance response; STN-DBS, Bilateral deep brain stimulation of the subthalamic nucleus; TOL, Tower of London; ToM, Theory of Mind; TMT, Trail Making Test; WCST, Wisconsin Card Sorting Test.

As shown in **Table II-2**, decision making is quite consistently impaired across neurodegenerative conditions. In IGT studies, results from FTD, HD and AD patients demonstrated decision making impairment that highlights the importance of the cortical and limbic structures in decision making under ambiguity. IGT deficits in PD patients appear to be dependent on prescribed dopaminergic medications that can contribute to dopaminergic overstimulation of the orbitofrontal-striatal circuits involved in reward-based behavior (Poletti et al., 2010). These findings emphasize the role of dopamine in mediating emotional and behavioral processes involved in decisions under ambiguity.

Decision making studies using the GDT, albeit few, reveal inconsistent findings for deficits in AD and PD samples. What seems to be common among all of these neurodegenerative populations is that executive functions are often compromised (Cummings, 1995; Cummings & Cole, 2002; Emre, 2003; Hodges & Miller, 2001; Neary et al., 1998; Rascovsky et al., 2007; Weintraub, Moberg, Culbertson, Duda, & Stern, 2004). However, despite the presence of executive

dysfunctions across neurodegenerative samples, few correlations were found between executive functions and decision making under ambiguity in the IGT. In the GDT, correlations with executive functions were found in three out of the five studies. One study (2010) found no executive function impairment in a PD sample, and another study (Rossi et al., 2010) did find impairment, but neither explicitly tested relationships to GDT performance. The three studies where GDT deficits were related to executive dysfunctions (e.g., set-shifting difficulties in card sorting tests), may imply degenerative processes-related disruptions in basal-ganglia-prefrontal circuitry underlie these deficits. Based on the evidence of decision making impairment in FTD, AD, PD and HD, and the brain regions known to be vulnerable to neurodegeneration in these conditions, one can assume that both prefrontal cortical and subcortical brain regions are implicated in decision making under ambiguity (IGT) and risk (GDT).

3. Hypotheses

Hypothesis 1: Based on the decision making impairments found in MS with tasks other than the GDT, MS patients will also be impaired in the GDT, and especially so, those in more advanced disease stages.

Hypothesis 2: The GDT has been found to covary more strongly with executive functions than the IGT in various patient populations as well as in healthy controls. Therefore, GDT deficits in MS will also covary with executive dysfunctions.

Hypothesis 3: MS is associated with widespread CNS pathology, including neurodegenerative changes. Given that decision making impairments, including those measured with the GDT, were previously reported in primary neurodegenerative conditions, MS-related brain atrophy will covary with GDT deficits.

III. MATERIALS AND METHODS

1. Participants

A phone screen was conducted with MS patients and healthy control participants to ensure their eligibility. Patients were recruited through the Northern Alberta Multiple Sclerosis Patient Care and Research Clinic at the University of Alberta Hospital with the help of neurologists Drs. Kenneth Warren, Christopher Power, and Gregg Blevins, Dept. of Neurology, University of Alberta. Controls were recruited by print/online advertisements in Edmonton's Metro Newspaper and Edmonton's Kijiji Classifieds.

Exclusion criteria for both patients and control participants were:

a) Present or past major neurological conditions (apart from MS for patients) including epilepsy, stroke/transient ischemic attack, Parkinson's disease, moderate to severe head trauma, dementia, encephalitis or meningitis.

b) Present or prior major health conditions such as cancer (other than skin cancer), heart attack or surgery, an adverse reaction to general anaesthesia, liver or kidney disease, lupus, Type 1 Diabetes.

c) MS patients on corticosteroids for the treatment of a MS relapse.

d) Uncorrected vision or hearing problems.

e) Primary psychiatric disorders with significant impact (e.g., hospitalization) such as psychosis/schizophrenia, major depression or anxiety disorders

f) Present or past electroconvulsive therapy or neurosurgery.

g) Significant alcohol/drug abuse within the past 5 years.

h) Significant developmental disabilities such as a pervasive learning disability.

i) Non-fluency in English.

j) Inability to consent (i.e., individuals under legal guardianship).

Specific inclusion criteria for MS patients included:

a) An MRI-confirmed diagnosis for MS according to the revised McDonald criteria (see **Appendix A** for details).

b) RR or SP subtype of MS (i.e., primary progressive MS patients were not included).

c) EDSS score less than 7 (no pervasive motor difficulties).

d) A recent clinical MRI scan.

Five MS patients were excluded post hoc from my study for the following reasons: EDSS score was higher than 6.5 (2 patients); neuromyelitis optica (1 patient); history of severe head trauma (1 patient); corticosteroid injection immediately preceding testing (1 patient).

The University of Alberta Health Research Ethics Board approved the study and all participants provided written informed consent. Patient testing took place in a single individual test session at the Northern Alberta Multiple Sclerosis Patient Care and Research Clinic, University of Alberta. For controls, testing took place in a single individual test session in a testing room in the Research Transition Facility, University of Alberta. Patients and controls were compensated $30 for expenses they incurred in the context of their participation.

Our final sample consisted of 32 MS patients and 20 healthy controls. Demographic characteristics of this sample are presented in **Table III-1.**

Table III-1. *Demographic variables of the study sample.* Scores are presented as means (standard deviations) or frequency counts (percentages).

	Controls (n=20)	**Patients (n=32)**	**Test statistic**	**Significance**
Females	12 (60%)	24 (75%)	$\chi^2[1]=1.30$	n.s.
Age (years)	48.20 ± 11.04	50.81 ± 9.48	t[50]= 0.90	n.s.
Education (years)	14.70 ± 2.11	13.64 ± 1.70	t[50]= -2.00	†
Premorbid IQ[x]	110.20 ± 11.71	105.16 ± 12.16	t[50]= -1.48	n.s.

[x]:Shipley Institutes of Living Scales, verbal subtest; premorbid IQ-calculation based on Zachary, R.A., and Gorsuch, R.L. (1985); n.s.: non-significant; †= p <.1.

As can be seen from **Table III-1**, patients and controls were well-matched in age, gender and premorbid IQ. There was a non-significant trend towards higher education in controls compared to the patient subgroup.

I further split the patient group into degrees of disability according to the following system:

1. RR-1: Patients with RRMS and an EDSS score of less than 3.0, a score that indicates mild disability in 1 or minimal disability in 2 functional systems.
2. RR-2: Patients with RRMS and an EDSS score of equal or greater than 3.0, a score that indicates moderate disability in 1 or mild disability in 3 or 4 functional systems.
3. SP: Patients with SPMS.

A summary of these subgroups' demographics and disease-related variables is presented in **Table III-2**.

Table III-2. *Summary of controls and patient subgroups' demographic and disease-related variables.* Scores are given as means and standard deviations or frequency counts and percentages.

	Controls (n=20)	**RR-1 (n=13)**	**RR-2 (n=9)**	**SP (n=10)**	**Test Statistic**	**Significance**
Females	12 (60)	11 (84.62)	6 (66.67)	7 (70)	$\chi^2(3)=2.28$	n.s.
Age (years)	48.20 ± 11.04	52.00 ± 9.76	46.77 ± 10.73	52.89 ± 7.53	F(3,48)= 2.53	n.s.
Education (years)	14.70 ± 2.11	14.15 ± 2.08	13.22 ± 1.72	13.35 ± 0.94	F(3,48)= 1.88	n.s.
Premorbid IQ[x]	110.20 ± 11.71	110.85 ± 10.27	101.17 ± 15.33	101.35 ± 8.98	F(3,48)= 2.53	†
Age at Onset (years)	--	34.12 ± 9.17	35.06 ± 9.71	34.30 ± 11.22	F(2,29)= 0.03	n.s.
Disease duration (years)	--	17.16 ± 12.76	11.28 ± 7.48	18.40 ± 8.40	F(2,29)= 1.32	n.s.
EDSS Score	--	1.58 ± 0.70	4.11 ± 1.43	5.2 ± 1.44	F(2,29)= 28.40	**

[x]: Shipley Institutes of Living Scales, verbal subtest, Premorbid IQ-calculation based on Zachary, R.A., and Gorsuch, R.L. (1985); RR-1: Relapsing-remitting MS patients with EDSS (Expanded Disability Status Scale) scores 0-2.5; RR-2: Relapsing-remitting MS patients with EDSS scores ≥ 3; SP: Secondary Progressive MS patients; n.s.: non-significant; †: $p < .1$; *: $p < .05$; **: $p < .001$.

As can be seen from **Table III-2**, patient subgroups were largely well-matched in demographic variables, although there was a trend towards higher

premorbid IQ in controls and RR-1 compared to the RR-2 and SP patient subgroups. As intended, patient groups differed substantially in EDSS score.

The clinical MRI scans in my study had been acquired as part of the patients' ongoing treatment protocol. Therefore, it was difficult to ensure a close temporal proximity between the dates of testing and the scan dates in all cases. One patient (019) had a MRI scheduled following participation in this study but the appointment got cancelled, so no neuroimaging data is available for this individual. A summary of the MR data is presented in **Table III-3**.

Table III-3. *Details on magnetic resonance images obtained from patients*

Patient ID	Time between Scan and Test Date (weeks)	Location	Scan Thickness (mm)
001	125.57	C	5
002	8	A	5
003	8.57	A	5
005	11.43	A	5
006	184.5	A	5
008	55.14	A	5
010	3.14	D	3
011	5.29	A	5
012	68.71	B	5
013	36.71	B	5
014	3.86	B	5
015	48.43	A	5
016	15.86	A	5
017	146.14	A	5
018	29.43	A	5
019	-	-	-
020	58.43	A	5
022	10.86	A	5
023	111.86	A	5
024	11.14	A	5
025	143.14	E	5
026	67.14	A	5
027	6.14	A	5
029	12.57	A	5
030	10.57	A	5
032	10	A	5
033	3.29	A	5
035	43	B	5
036	113.57	A	5.5
037	112	A	5
038	33.14	A	5
039	33.57	A	5
	Mean= 42.51 (SD= 57.49)		

A: University of Alberta Hospital; B: Royal Alexandra Hospital; C: Insight Medical Imaging, Meadowlark; D: Medical Imaging Consultants, Century Park; E: Misericordia Hospital; SD: Standard deviation

The MR scans were acquired from five different scan sites across Edmonton on different models of conventional 1.5T MR scanners, usually with a scan thickness of 5 mm. The average time between the MR scan and the test date was 42.51 weeks (SD=57.49) or 10.62 months.

Participants were currently taking a variety of prescription medications for health conditions not part of the exclusion criteria, including high blood pressure, high cholesterol, heartburn and acid reflux, osteoarthritis and bone density, asthma, and gastrointestinal/urological concerns. Participants on the antidepressants bupropion, selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) were permitted. Since it is common for MS patients (especially SPMS patients) to be prescribed psychotropic drugs for symptom management (i.e., insomnia, neuropathic pain), these patients could not be excluded from the study, even though these medications have the potential to impact cognition. Thus, some MS patients were on (low doses of) benzodiazepines and anticonvulsants. Current self-reported medications were obtained from all 32 MS patients. An overview on disease modifying (see **Table III-4**) and symptom management drugs prescribed to the MS patients (see **Table III-5)** is presented below.

Table III-4. *MS disease-modifying treatment at the time of the study*

MS Subtype	EDSS Score	ID	Interferon Beta- 1a or 1b	Glatiramer Acetate
RR-1	0.0	020	YES	-
RR-1	1.0	032	-	YES
RR-1	2.0	010	-	YES
RR-1	2.0	017	YES	-
RR-1	2.0	035	YES	-
RR-2	3.0	011	-	YES
RR-2	3.0	036	YES	-
RR-2	3.5	016	-	YES
RR-2	6.5	018	-	YES
Total			**4**	**5**

RR-1: Relapsing-remitting MS patients with EDSS (Expanded Disability Status Scale) scores 0-2.5; RR-2: Relapsing-remitting MS patients with EDSS scores ≥ 3.

In total, 9 RRMS patients (28.13%) were currently prescribed a disease-modifying drug (i.e., Interferon Beta or Glatiramer Acetate), with no patients prescribed both Interferon Beta and Glatiramer Acetate simultaneously. No SPMS

patients were prescribed any disease-modifying drugs; this is to be expected given that the indication for these medications is for patients with a relapsing, and non-progressive, disease course.

Table III-5. *Type and dosage for medications prescribed for the management of MS patients' symptoms*

MS Subtype	EDSS Score	ID	Pain	Sleep/ Anxiety	Depression	Muscle Spasticity
RR-1	0.0	020	-	-	Bupropion 300 mg[1]	Baclofen 20 mg[2]
RR-1	2.0	005	-	Zopiclone unknown dose	Venlafaxine 75 mg[2]	-
RR-1	2.0	006	-	-	Venlafaxine 75 mg[1]	-
RR-1	2.0	010	-	-	Venlafaxine 75 mg[1]	-
RR-1	2.0	017	-	Zopiclone 7.5 mg[1]	Venlafaxine 150 mg[1]	Baclofen 20 mg[2]
RR-1	2.0	024	-	-	Paroxetine 20 mg[1]	-
RR-2	3.0	001	-	-	Fluvoxamine 50 mg[2], Bupropion 150 mg[1]	-
RR-2	6.5	018	Gabapentin 300 mg[3]	-	-	Baclofen 20 mg[4]
RR-2	6.5	030	-	-	-	Baclofen 20 mg[1]
SP	3.0	027	-	Zopiclone 10 mg[1]	-	Baclofen 10 mg[2]
SP	3.0	029	-	-	-	Baclofen 10 mg[1]
SP	4.5	015	-	Clonazepam 1 mg[1]	Citalopram 60 mg[1]	-
SP	6.0	013	-	-	-	Baclofen 15 mg[1]
SP	6.0	023	-	-	Desvenlafaxine 100 mg[1]	-
SP	6.0	037	Gabapentin 40 mg[3]	-	Paroxetine 20 mg[1]	Tizanidine 4 mg[1]
SP	6.5	002	-	Flurazepam 30 mg[1]	Trazodone 50 mg[1]	Baclofen 20 mg[4]
Total			**2**	**5**	**11**	**9**

RR-1: Relapsing-remitting MS patients with EDSS (Expanded Disability Status Scale) scores 0-2.5; RR-2: Relapsing-remitting MS patients with EDSS scores ≥ 3; SP: Secondary progressive MS patients; EDSS: Expanded Disability Status Scale; [1]= 1/day; [2]= 2/day; [3]= 3/day; [4]= 4/day

Twenty-one patients (65.63%) were taking at least one prescription medication for MS and/or neurological concerns. Ten patients (31.25%) were on

more than one medication. In total, two patients (6.25%) were on a medication for neuropathic pain, five patients (15.63%) were prescribed a medication for sleep and/or anxiety, twelve patients (34.38%) were prescribed antidepressants, and nine patients (28.13%) were on anti-spasticity or muscle relaxation medications.

2. Neuropsychological test battery

Neuropsychological tests and questionnaires were administered in a single test session. Apart from the GDT, tests were selected either based on their inclusion in neurocognitive screening batteries for MS (i.e., BRB-N and/or MACFIMS) (Gainotti, 2006; Ghaffar & Feinstein, 2007; Rao, 1990) or due to my goal of providing an assessment of executive functions that were assumed to play a role in GDT performance. Self-report questionnaires on mood, fatigue, perceived dysexecutive functions and perceived disability were administered to patients only. Tests were administered in a fixed order as shown in **Table III-6**.

Table III-6. *Test sequence and estimated administration time*

Test	Administration Time (minutes)
Cognitive Tests	
Symbol-Digit Modalities Test	3
Verbal Selective Reminding Task (immediate recall)	12
Game of Dice Task	10
Paced Auditory Serial Addition Test- 3”	10
Nine-hole Pegboard	3
Tower of Hanoi	6
Verbal Selective Reminding Task (delayed recall)	2
BREAK	
Wisconsin Card Sorting Test- 64 card version	15
Digit Span (Forward & Backward)	6
Controlled Oral Word Association Test	4
Shipley Institute of Living Scales (vocabulary subtest)	11
Psychosocial Questionnaires	
Hospital Anxiety and Depression scale	6
Dysexecutive Questionnaire (self)	10
Fatigue Assessment Instrument	6
London Handicap Scale	5
	Total Administration Time= 106 minutes

General features of the test instruments are given in the following.

2.1. Game of Dice Task (GDT; Brand et al., 2002)

The main test of interest in this study was the computerized GDT, used to assess decision making under risk. The task has been described in detail in **Section II-2.1.2** in the introduction (see also **Figure II.3**). The main outcome measure is the GDT net-score (safe minus risky choices). In addition, I also calculated the number of times a participant switched between risky and safe choices (total number of shifts) as well as their tendency to perseverate on either safe or risky choices (details see **Section IV-4.5**).

2.2. Shipley Institute of Living Scales (SILS; Zachary, R., 1986)

The SILS is a paper-and-pencil test of vocabulary and verbal abstraction (the verbal abstraction portion was omitted here) that is highly correlated with scores from more comprehensive IQ testing (Zachary, R., 1986) such the full-scale IQ score derived from the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981). For the vocabulary portion, participants have to indicate which one of four provided responses is a synonym to a target word. The score is an estimate of a patient's premorbid intelligence, assuming that crystallized intelligence, largely based on premorbid education levels, is preserved despite the neurological condition or aging processes. The SILS/estimate of premorbid IQ is not found in either the BRB-N or MACFIMS battery, but has been included in several studies investigating cognitive performance in MS (for example, (Aupperle, Beatty, Shelton Fde, & Gontkovsky, 2002; Beatty et al., 1995; Smith, M. M. & Arnett, 2005).

2.3. Symbol-Digit Modalities Test (SDMT; Smith, A., 1982)

The SDMT is a measure of working memory and speed of information processing, visual tracking and motor coordination. Participants are required to substitute numbers for symbols according to a key provided on a response form. The score is the total number of correct items that a participant is able to record in 90 seconds. The SDMT is administered in both the BRB-N and the MACFIMS batteries. The SDMT is often considered to be the most sensitive measure to

cognitive impairment in MS (e.g., Strober et al., 2009), and is part of the Multiple Sclerosis Functional Composite (MSFC; Fischer, Rudick, Cutter, & Reingold, 1999), a multidimensional clinical outcome measure that includes quantitative tests of leg, arm and cognitive function. Performance in this test has also been found to be correlated with global brain atrophy in MS patients (Benedict, Carone, et al., 2004; Benedict, Weinstock-Guttman, et al., 2004; Christodoulou et al., 2003).

2.4. Verbal Selective Reminding Test (SRT), short form (Hannay & Levin, 1985)

The SRT is a measure of immediate and delayed verbal memory and new learning. The short form of this test provides 12 words across 6 trials that are selectively rehearsed by the participant until they are memorized. That is, only words not recalled on the immediately preceding trial are presented on the following trial as a reminder. After six of these trials and a delay of about 20-30 minutes, the participant is asked to recall all words, without being reminded of any of them again. Total correct recall across all immediate recall trials, continuous long term retrieval (words that were recalled without additional reminding), total number of extra-list intrusions, and total number of words recalled after the delay were analysed here. This test is also used in the BRB-N, and characterizes the memory impairment in MS patients well, especially the continuous long term retrieval score. The SRT has also revealed that defective retrieval, more so than encoding, may underlie MS patients' memory problems (Beatty et al., 1996).

2.5. Paced Auditory Serial Addition Test (PASAT; Gronwall, D. & Sampson, 1974; Gronwall, D. M., 1977)

The PASAT assesses auditory information processing speed and flexibility as well as calculation ability. Participants hear a standardized recording of a series of single-digits at the rate of one number every 3 (or 2) seconds, and are required to add sequential pairs so that each digit is added to the digit immediately preceding it. The outcome score is the total number of correct responses. I only

used the 3-second version of the test in the current study. The PASAT is included in both the BRB-N and the MACFIMS batteries and was also found closely linked to measures of brain atrophy in MS patients (Lockwood, Linn, Szymanski, Coad, & Wack, 2004).

2.6. Nine-Hole Pegboard (Mathiowetz, Weber, Kashman, & Volland, 1985)

The nine-hole pegboard is a measure of finger dexterity and motor coordination. This is a timed task that requires the participant, with one hand, inserts nine pegs one at a time and as quickly as possible in the holes of the pegboard. Once all of the pegs are inserted, the participant then removes the pegs as quickly as possible one at a time. This test is first performed with the dominant hand followed by the non-dominant hand. The outcome score is the total time to complete the task (including both insertion and removal). Due to early administration errors in my study, I did not properly record removal times, and as a result, we only had insertion times for some patients. Therefore, I used insertion time here. This test is not included in either the BRB-N or MACFIMS battery; however, it is one of three tests used in the MSFC score (Fischer et al., 1999).

2.7. Tower of Hanoi (TOH; Goel & Grafman, 1995)

The TOH is a measure of planning, problem-solving, temporal ordering, and inhibition, all processes that are a part of executive functions. The task consists of three rods, and a number of disks (3, 4, or 5 disk trials that increase in difficulty) of different sizes that can slide onto any rod. The task starts with the disks stacked in ascending order of size on one rod, the smallest at the top, thus making a conical shape. The objective of the task is to move the entire stack of disks to another rod, obeying a few particular stacking rules (e.g., no larger disk can rest on a smaller disk). The completion time and the number of attempts to completion are recorded, and these are the scores that are produced across the 3 different trials. Although the TOH is not part of the BRB-N or MACFIMS battery, it is a measure of executive function that was shown to covary with the GDT in a

previous patient study (Brand, Kalbe, et al., 2004), and MS patients have been found to be impaired in the TOH (e.g., Arnett et al., 1997).

2.8. Wisconsin Card Sorting Test (WCST; Berg, E. A., 1948; Grant & Berg, 1948), 64-card version (Kongs, Thompson, Iverson, & Heaton, 1993)

The WCST is a classic measure of executive functions, including strategic planning, set-shifting, mental flexibility, as well as inhibition. The participant is presented with four stimulus cards that display designs that differ in three features (i.e., color, shape and number). The participant is given a stack of additional cards and asked to match the next card of their deck to one of the stimulus cards based on one pre-determined feature. The participant is not told how to match the cards but only given feedback after each sort regarding whether their last match was correct or incorrect. During the course of the test, the matching rules change, unannounced to the participant. The most commonly used outcome scores of the WCST are the total number of correct matches and the number of matching errors, particularly, perseverative errors (i.e., persisting to match cards on a matching rule that is no longer valid, despite negative feedback). The WCST is not part of the BRB-N or MACFIMS battery; however, since it is a rather comprehensive measure of executive function, and has been correlated with the GDT in studies with other patient samples (Bagneux et al., 2012; Brand, Fujiwara, et al., 2005; Brand, Kalbe, et al., 2005) as well as has shown MS-related impairment (e.g., Nagy et al., 2006), I included it here. For time-economical reasons, I chose the 64-card version.

2.9. Digit Spans (Wechsler, 1997)

The Digit Span Forward is a measure of short term memory. Participants listen to a sequence of digits and must immediately repeat them back. If they do this successfully for at least one of two different sequences of the same number of digits, they are given a one-digit longer sequence to repeat back. Digit Span Backward is a measure of working memory. Participants also listen to successively longer digit sequences; however, here their task is to recall the items

in reverse of the presented order. Outcome scores from both subtests are the number of correct trials. Digit spans are not part of the BRB-N or MACFIMS battery. The backward digit span was of specific interest in my study since it assesses working memory, i.e., an aspect of executive functions (e.g., Miyake et al., 2000).

2.10. Controlled Oral Word Association Test (COWAT; Borkowski et al., 1967)

The COWAT is a measure of verbal or phonemic fluency and assesses word generation ability, executive functions, divergent thinking and speed of information processing. Participants are asked to name as many words as they can that begin with one of three stimulus letters (F, A, or S, given one at a time), within one minute. Participants are provided with various rules on the words they are permitted to recall (e.g., non-allowed words include capitalized words or names, words starting with the same word stems). Outcome scores are the total number of correct words generated, number of perseverations (word repeats) and the number of intrusions. Similar tests of verbal fluency as the COWAT are included in the BRB-N and MACFIMS battery.

2.11. Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)

The HADS is a self-report screening tool that is often used to identify emotional distress in patients with physical conditions (Brennan, Worrall-Davies, McMillan, Gilbody, & House, 2010). In the HADS, participants read a statement that relates to behaviour common to either anxious or depressive mood and indicate the degree (on a scale of 0 to 3) that is a common experience for them. Outcome scores are one score for anxiety and one score for depression. The HADS was included to give an estimate of mood symptoms in the patients, as these are common concomitants of MS that may also influence decision making independently of MS. It should be noted that the HADS has been criticized since its factor structure does not clearly separate the two assumed underlying constructs, i.e., anxiety versus depression (e.g., Cosco, Doyle, Ward, & McGee,

2012). Thus, elevated HADS scores may indicate higher levels of emotional distress, subsuming depression-related and anxiety-related concerns.

2.12. Dysexecutive Questionnaire (DEX; Burgess, Alderman, Wilson, Evans, & Emslie, 1996)

The DEX is a self-report and informant measure of twenty common behavioral difficulties associated with executive dysfunction after frontal lobe damage. Although I initially intended to use both self-and informant-rated versions of the DEX, due to recruitment difficulties of informants, only the self-rated version could be included. Participants read statements that suggest executive dysfunction and indicate the degree that they experience these using a 5-point Likert scale. Bodenburg and Dopslaff (2008)'s norms were used to analyze the DEX. Using factor analytical approaches, the authors combined DEX items into four factors and one total score and then provide cut-off scores (for additional details on item-subscale relationships see (Bodenburg & Dopslaff, 2008). Factor (F)1 measures the perceived ability to initiate and sustain ("initiate/sustain") actions in a broad sense. F2 measures perceived impulse control and sequencing ("impulse control/sequencing") of information or actions. F3 measures the individual's psychophysical and mental excitability ("excitability"). F4 measures the perceived ability to incorporate social standards into interpersonal interactions ("social"). Outcome scores were the four factor scores as well as an overall DEX score.

2.13. Fatigue Assessment Instrument (FAI; Schwartz et al., 1993)

The FAI is a self-report measure that requires participants to read statements about fatigue and its symptoms. Using a 7-point Likert scale, they indicate the degree that they agree with the given statement. The FAI assesses several aspects of fatigue (F1: overall fatigue severity [severity], F2: situational triggering of fatigue [situation], F3: psychological consequences of fatigue [psychological], F4: likeliness of one's fatigue to respond to rest/sleep [sleep]). Outcome scores used here were totals in each of the four factor scores.

2.14. London Handicap Scale (LHS; Hardwood & Ebrahim, 1995)

The LHS is a self-report measure used to determine the effect of chronic disorders on a person's functional ability across six major domains of daily life. Participants complete the questionnaire using a 6-point interval scale indicating the severity of their impairment in each domain. Outcome scores comprise an overall score as well as sub-scores for each of the following domains: mobility (how one gets from one place to another, using any help, aid or means of transport), physical independence (looking after oneself with daily activities such as cooking, getting dressed, etc.), occupation (can relate to paid or unpaid work), social integration (getting on with people one would be around/meet in a normal day), orientation (awareness of one's surroundings), and economic self-sufficiency (affording the things one needs).

3. Linear measures of ventricular enlargement

Clinical MR images were analyzed with ClearCanvas Workstation Version 2.0. Radiologist Dr. Derek J. Emery (Neuroradiologist, Department of Diagnostic Imaging, University of Alberta) supervised the linear measurements on the MR scans. Linear measurements were performed on a single axial slice, specifically the most caudal axial T2-weighted slice where the frontal horns appeared to reach maximal width (Butzkueven et al., 2008). All measurements were performed with a digital ruler included in the software, adhering to the method outlined by Butzkeuven et al. (2008) (see **Figure III-1** for a typical image tracing):

a) **Frontal Horn Width (FHW):** Defined as the maximal distance between the lateral borders of the frontal horns of the lateral ventricles.
b) **Transverse Width (TW):** Defined as the minimum distance separating the inner tables of the skull at the level of the caudate nuclei.
c) **Intercaudate Distance (ICD):** Defined as the minimum distance between the medial borders of the head of the caudate nuclei.
d) **Intercaudate Ratio (ICR):** Calculated by dividing the ICD by TW.

e) **Third Ventricle Width (TVW):** Defined as the maximum distance between the lateral borders of the middle of the third ventricle where the ventricle's borders were nearest to parallel.

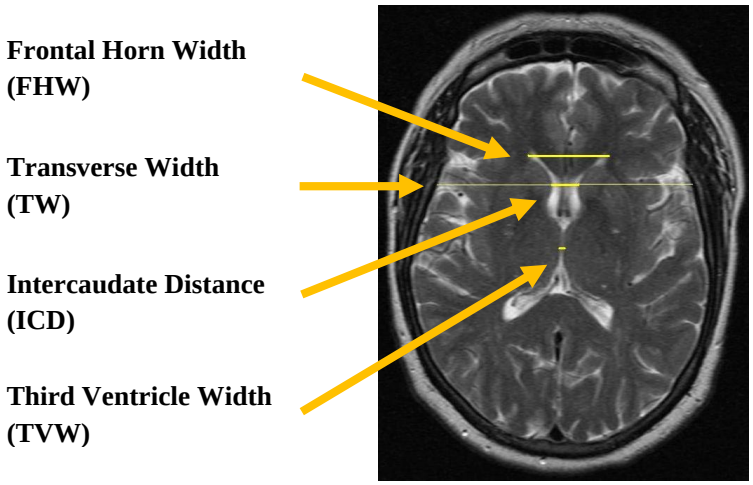

Figure III-1. *Example of T2-weighted axial MR slice selected for measurements of the linear atrophy markers*

Patients' MR scans were acquired from their clinical health records and I did not perform scans on the healthy controls within the study context. In order to nevertheless quantify patients' MR parameters, I analysed similar quality historical MR scans of patients who had presented for neurological examination (i.e., individuals with atypical/unusual headache whose MRI was ordered to rule out any structural abnormalities), but whose clinical MR was deemed normal by a radiologist. A total of 20 such control patient scans were acquired through Dr. Christopher Power and were analysed in the same way as the MS patients' scans. The 20 control patients were statistically matched to the MS patients with regard to sex distribution ($\chi 2[1]=1.14$, $p > .1$; MS-patients: N = 23/8 female/male; control patients: N = 12/8 female/male) and age ($t[49] = 0.88$, $p > .1$; MS-patients: Age= 50.5 ± 9.43 years; control patients: Age= 47.8 ± 12.08 years).

Each of the measurements (FHW, ICD, ICR, and TVW) were taken three times for each MS patient and control patient, and the mean of these three measures was used. The intra-class coefficients for each of the measures were

above .9, indicating high intra-rater reliability. In addition, a second rater applied the same measures on all scans. Inter-rater reliability on the averaged measures showed similarly high intra-class coefficients (FHW= .89; ICD= .98; ICR= .98; TVW= .97).

4. Composite scores of cognitive performance

To minimize false positive results (Type I errors), performance in the relatively large number of cognitive tests and scores within each test was combined and summarized in composite scores of cognitive performance. There are several approaches to calculate such composite scores, among them data-driven approaches (e.g., Principal Component Analysis, Exploratory Factor Analysis, Confirmatory Factor Analysis [Bartholomew, Steele, Galbraith, & Moustaki, 2008], Item Response Theory [Embretson & Reise, 2000]) are preferable. However, due to the limited sample size, data-driven approaches used for the generation of composite scores were not feasible here. Instead, I selected tests and scores within each test representative of the assessed cognitive domains, based on theoretical considerations (see below for more details). Of note, I acknowledge that such approach does not account for the potential (overt or latent) overlap of test scores between cognitive domains (e.g., components of executive functions exerting their influence on memory performance). To account for such potential overlap, a global cognitive functioning score was devised.

Four composite scores were calculated: Speed of Information Processing (SOIP), Memory (MEM), Executive Functions (EF), Global Cognitive Functioning (Global: A combination of SOIP, MEM, EF). In order to generate the composite scores, control participants' performance in each test score was first assigned to the respective domain. Controls' performance was then used to transform the patients' performance into z-scores relative using the formula:

$$zP = (meanC - meanP) / standard\ deviationC$$

where C denotes controls and P denotes patients. The direction of the subtraction was reversed in cases where higher scores indicate worse performance

(e.g., response times, error scores). Thus, a higher z-score in each of the composites always indicated better performance. The number of individual tests (and test scores per test) within each composite score could not be equated since assessment of executive functions was over-represented in my battery. The following variables were included in my composite scores:

Speed of Information Processing (SOIP)

- **a)** Symbol-Digit Modalities Test (SDMT); total correct
- **b)** Paced Auditory Serial Addition Test (PASAT); total correct
- **c)** Pegboard Total Insertion Time; average of dominant and non-dominant hand insertion time
- **d)** Digit Span Forward (DSF); total correct

Memory (MEM)

- **a)** Selective Reminding Test (SRT); immediate recall
- **b)** SRT; consistent long-term retrieval (words recalled throughout the task without prompting between trials)
- **c)** SRT; delayed recall

Executive Functions (EF)

- **a)** SRT; total number of intrusions
- **b)** Wisconsin Card Sorting Test 64-card version (WCST); total number of correct sorts
- **c)** WCST; total number of perseverative errors
- **d)** Verbal Fluency Test (COWAT); total number of correct words across all three task blocks F, A, and S
- **e)** Tower of Hanoi (TOH); time to complete task blocks
- **f)** Digit Span Backward (DSB); total correct

The "global" cognitive function score was derived by averaging the three composite scores listed above.

As mentioned, my test battery had a relative preponderance of tests selected to assess aspects of executive functions. This was because I expected relationships

between GDT performance and executive functions specifically, but not, for example, long-term memory functions (Labudda et al., 2009). Thus, the MEM composite score has to be interpreted cautiously, since it is derived from three variables of a single test, the SRT, assessing verbal long-term memory. Performance in one aspect of the SRT substantially influences performance in other SRT scores, and hence MEM scores might be inflated. Nevertheless, to retain some specificity while controlling the number of comparisons, I calculated and report domain-specific composite scores. The inclusion of tests and test variables in each of the composite scores was driven by theoretical considerations that are outlined below.

SOIP: Both, SDMT and PASAT are highly sensitive to deficits in information processing speed/attention and are considered core tests to assess these domains in MS (Iverson, Lovell, & Collins, 2005; Lezak, 1994; Ponsford & Kinsella, 1992). These tests can be used interchangeably in the assessment of processing speed deficits in MS patients (Drake et al., 2010). Including pegboard insertion time into the SOIP composite score was since both motor and cognitive slowing can point to underlying WM changes, e.g., in normal aging (Sanchez et al., 2008). Performance in the DSF reflects attention and passive maintenance of information in short-term memory (Wechsler, 1997) and may be specifically related to cognitive slowing in MS (Beatty et al., 1995).

MEM: I assessed memory performance with a single test, the SRT. The SRT has been extensively studied in MS and is included in MS-specific neuropsychological batteries (such as the BRB-N [Rao, 1990]). Although many scores can be obtained from the SRT, I included overall performance in immediate recall across all six trials, consistent long-term retrieval (recall of words without further prompting between trials) and delayed recall. Consistent long-term retrieval has been found to be particularly useful in memory assessment in MS (e.g., Rao et al., 1991).

EF: 'Executive functions' is an umbrella term to describe a variety of control and monitoring functions assumed to be associated with dorsal and lateral PFC regions (Shallice & Burgess, 1991; Stuss & Alexander, 2000). One influential theoretical model of executive functions by Miyake et al. (2000) is based on factor analytical considerations and the extraction of latent constructs across classic executive function tests. This model proposes a division of executive functions into three components: 'Inhibition', 'shifting', and 'updating'. However, a lack of differentiation between such subcomponents, i.e., a one-factorial nature of executive functions, has also been supported (e.g., in aging: (Salthouse, Atkinson, & Berish, 2003). Such one-factorial organization of executive functions seems especially likely in conditions of impairment, e.g., patients with frontal lobe lesions (Roca et al., 2010) or aging-related cognitive decline (de Frias, Dixon, & Strauss, 2009). My goal with the calculation of composite scores was to reduce the number of variables in my analyses. Therefore, I decided to combine critical test scores into one, rather than three different, composite scores of executive functions, acknowledging that my battery spanned all three potential components. With this is mind, intrusions in the SRT were included in this EF composite score since intrusions in verbal list learning paradigms may indicate deficits in 'inhibition' (e.g., Chan, A. S. et al., 2009; Mahone, Koth, Cutting, Singer, & Denckla, 2001). Furthermore, performance in the TOH was included. The TOH was part of Miyake et al.'s (2000) derivation of the 'inhibition' component of executive functions. The conventional calculation of performance in the TOH summarizes the number of moves required for successful completion of all trials (i.e., task versions using three, four, five disks [Goel & Grafman, 1995]). However, half of the patients and 25% of the controls did not successfully complete the five disks trial. Therefore, their scores would have had to be omitted in calculating the total number of moves across all trials. As an alternative, I used the time required for the completion (attempt) across all trials, and in the event of failed trials, I replaced missing values by the maximum time allotted per trial (300 seconds). This allowed retaining information about TOH performance across all three trials in all participants. The WCST is considered a hallmark measure of

executive functions and WCST perseverative errors in particular are considered the most sensitive measure of the shifting/switching component of executive functions (Greve, Stickle, Love, Bianchini, & Stanford, 2005; Miyake et al., 2000). Verbal fluency, although also a measure of lexical and language abilities, is another prominent measure of executive function. Phonemic verbal fluency (as assessed with the COWAT) is assumed to tap into the 'shifting' component of executive functions (Miyake et al., 2000). Several fluency tasks are included in the Delis Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001; Delis, Kramer, Kaplan, & Holdnack, 2004). Phonemic verbal fluency is impaired in patients with focal frontal lobe lesions and this association may even supersede that between the WCST and frontal brain damage (Henry, J. D. & Crawford, 2004). Finally, DSB was included in the executive function composite score and assesses working memory or the 'updating' component of executive functions (Miyake et al., 2000). Working memory functions are subserved by DLPFC regions in humans (Callicott et al., 1999; Owen et al., 1999) and animals (Castner, Goldman-Rakic, & Williams, 2004; Petrides, 1995, 2005) and are impaired after lesions in those areas (D'Esposito & Postle, 1999; Muller, Machado, & Knight, 2002; Petrides, 1995).

Since the MS patients' cognitive performance here is compared to that of study controls', the controls' neuropsychological performance based on published norms was assessed to ensure the control group performed normally. Using standardized norms for each test, **Appendix B** shows that the controls' had mean z-scores ranging from -.74 to .47, with the mean scores of most tests being close to 0, indicating average neuropsychological performance.

5. Statistical Analyses

All statistical analyses were conducted using SPSS 15.0. All variables were first tested for normality using the Kolmogorov-Smirnov test (K-S test). Non-parametric equivalents were used instead of parametric tests for variables that were non-normally distributed (e.g., U-test instead of t-Test).

Two separate sets of analyses are presented to compare patients with controls. First, I report performance in all MS-patients contrasted against controls. Differences were assessed with t-tests (or U-tests). In the case of unequal group variances, as indicated by Levene's test, the unequal variance t-test correcting degrees of freedom, was applied (incorporated in SPSS). Relationships were tested with Pearson correlations or Spearman rank correlations, if indicated.

Secondly, I divided patients into subgroups according to their disability status (as described in Participants **Section III-1**: RR-1, RR-2, SP) and report subgroups' performance levels against those of controls. Differences between controls and each of these subgroups were assessed with one-way ANOVA (or Kruskal-Wallis tests, where indicated). Significant omnibus effects were followed up by post-hoc tests comparing each patient subgroup against controls (but not against each other), controlling for multiple comparisons (Dunnett t-tests). For all ANOVAs, in case of variance inhomogeneity as indicated by Levene's test, the Welch test was applied to correct F-ratios and degrees of freedom. In this case, manual U-tests were used to compare controls to each subgroup of patients, Bonferroni-correcting the alpha level (e.g., in case of three comparisons such as controls vs. RR-1, controls vs. RR-2, controls vs. SP: alpha = .05 / 3 = .0167). The core analyses involving differences in GDT performance among subgroups were complemented by moderated regression analyses to test potential influences of group-differences in demographics (i.e., premorbid IQ or years of education) on GDT performance. Relationships between variables within subgroups were tested with Spearman rank correlations, this is preferable in small samples (Gautheir, 2001). Relationships between brain atrophy measures and cognitive variables were assessed with partial correlations controlling for age and gender. A p-value of $p < .05$ was the significance threshold for all statistical analyses, unless otherwise stated.

IV. RESULTS

1. Performance in individual neuropsychological tests

Table IV-1 provides an overview of patients' and controls' scores in the individual neuropsychological test variables that were later included in the cognitive composite scores.

Table IV-1. *MS patients' neuropsychological test results and comparison with controls.* Scores are presented as means (standard deviations) or medians (range).

Composite Score	Test/test variable	Controls (n=20)	Patients (n=32)	Test Statistic
SOIP	SDMT	52.30 (12.34)	44.29 (9.63)	t[49]= -2.60*
	PASAT 3"	48.80 (10.44)	43.44 (11.06)	t[50]= -1.74
	Pegboard (Dominant/Non-dominant hand)	27.40 (4.56)	33.95 (9.87)	t[46.86]= -3.24*
	DSF	11.10 (1.92)	9.94 (1.83)	t[50]= -2.19*
MEM	SRT Total Recall	53.65 (6.85)	39.09 (10.96)	t[49.99]= -5.02**
	SRT Consistent Long Term Retrieval	36.85 (13.14)	18.00 (13.24)	t[50]= -2.96*
	SRT Delayed Recall	8.10 (2.43)	5.53 (2.55)	t[50]= -3.58**
EF	SRT Intrusions	Md.=0.00 Rg.= 0-12	Md.=1.00 Rg.= 0-6	U=230.00
	TOH (Time)	317.25 (139.78)	384.81 (132.47)	t[49]= -1.74
	WCST Total Correct	50.65 (3.88)	47.13 (7.71)	t[48.29]= -2.18*
	WCST Perseverative Errors	6.45 (2.11)	8.44 (5.65)	t[48.51]= 1.46
	COWAT	46.50 (10.59)	36.69 (9.10)	t[50]= -3.55**
	DSB	7.65 (1.79)	6.22 (2.01)	t[50]= -2.60*

SOIP: speed of information processing, MEM: memory, EF: executive functions, SDMT: Symbol-Digit Modalities Test, PASAT: Paced Auditory Serial Addition Test 3'' version, Pegboard: Nine-Hole Pegboard Test, DSF: Digit Span Forward, SRT: Selective Reminding Test, COWAT: verbal fluency test, DSB: Digit Span Backward, TOH: Tower of Hanoi, WCST: Wisconsin Card Sorting Test (64-card version), Md.: median, Rg.: range; *: $p < .05$, **: $p < .01$.

As can be seen in **Table IV-1,** patients had impaired performance as compared to controls in several measures of attention, and executive functions, and most pronounced deficits were found in memory as assessed with the SRT. **Table IV-2** provides an overview of patients subgroups' and controls' scores in the individual neuropsychological test variables.

Table IV-2. *Patient subgroups' neuropsychological test results and comparison with controls.* Scores are means (standard deviations) or medians (range).

Composite Score	Test/ test variable	Controls (n=20)	RR-1 (n=13)	RR-2 (n=9)	SP (n=10)	Test statistic
SOIP	SDMT	52.30 (12.34)	48.31 (8.87)	40.00*[1] (9.24)	42.50 (9.71)	F[3,47]= 3.47*
	PASAT 3"	48.80 (10.44)	48.54 (5.38)	34.67*[1] (12.49)	44.70 (11.31)	F[3,48]= 4.65*
	Pegboard (Dominant & Non-dominant hand)	27.40 (4.56)	32.25 (9.29)	32.80 (5.48)	37.19*[1] (13.30)	F[3,48]= 3.35*
	DSF	11.10 (1.92)	10.38 (1.98)	10.00 (1.50)	9.30 (1.89)	F[3,48]= 2.24
MEM	SRT Total Recall	53.65 (6.85)	42.08*[2] (11.62)	39.11*[2] (12.43)	35.20*[2] (8.15)	F[3,20.16]= 14.31**[2]
	SRT Consistent Long Term Retrieval	36.85 (13.14)	21.00*[2] (14.50)	19.11 (16.44)	13.10*[2] (6.49)	F[3,22.46]= 13.85**[2]
	SRT Delayed Recall	8.10 (2.43)	6.46 (2.50)	5.11*[2] (2.89)	4.70*[2] (2.11)	F[3,22.09]= 5.67*[2]
EF	SRT Intrusions	Md.= 0 (Rg.=0-12)	Md.= 1 (Rg.=0-3)	Md.=0 (Rg.=0-4)	Md.=1 (Rg.=0-6)	χ^2[3]= 5.26
	TOH (Time)	317.25 (139.78)	417.67 (118.32)	390.67 (179.25)	340.11 (95.56)	F[3,47]= 1.61
	WCST Total Correct	50.65 (47.13)	48.92 (8.35)	44.11 (8.42)	47.50 (5.89)	F[3,19.04]= 2.07[2]
	WCST Perseverative Errors	6.45 (2.11)	7.85 (5.06)	8.44 (4.10)	6.90 (2.92)	F[3,48]= 0.83
	COWAT	46.50 (10.59)	38.15 (10.37)	36.33*[1] (9.14)	35.10*[1] (7.84)	F[3,48]= 4.28*
	DSB	7.65 (1.79)	6.77 (1.79)	5.78 (2.82)	5.90*[2] (1.37)	F[3,21.83] = 3.14*[2]

[1]: Post-hoc tests were Dunnett t-tests against controls; [2]:Variance inhomogeneity indicated by Levene's test: Welch adjustment of F-ratio and degrees of freedom, post-hoc tests were Bonferroni-corrected U-tests against controls; SOIP: speed of information processing, MEM: memory, EF: executive functions, SDMT: Symbol-Digit Modalities Test, PASAT: Paced Auditory Serial Addition Test 3'' version, Pegboard: Nine-Hole Pegboard Test, DSF: Digit Span Forward, SRT: Selective Reminding Test, COWAT: verbal fluency test, DSB: Digit Span Backward, TOH: Tower of Hanoi, WCST: Wisconsin Card Sorting Test (64-card version), Md: median, Rg: Range *: $p < .05$, **: $p < .01$.

Significant differences in the RR-1 subgroup were confined to memory in the SRT. Moreover, the SRT generally showed most pronounced impairment spanning all subgroups. The RR-2 and SP subgroups underperformed compared to controls in several tests of information processing speed and executive functions. Of note, the RR-2 subgroup was the only subgroup with impairment in the cognitive processing speed tasks (SDMT, PASAT 3''), while SP patients showed motor-slowing in the Nine-hole Pegboard. With regard to single executive function tests, neither the WCST nor the TOH were statistically impaired across subgroups, but both the RR-2 and SP subgroups were impaired in verbal fluency (COWAT) and the SP subgroup also showed impairment in working memory (DBS).

2. Performance in cognitive composite scores

Table IV-3 provides all MS patients' performance in the composite scores, indicating significant differences to controls.

Table IV-3. *MS patients' performance in composite scores of cognitive functions.* Scores are mean z-scores (standard deviations), based on study controls' means.

	Mean z-scores (n=32)	**Test statistic**
SOIP	-0.81 (0.81)	t[50]= -3.58**
MEM	-1.54 (1.16)	t[50]= -5.02**
EF	-0.63 (0.69)	t[50]= -3.41*
Global	-0.93 (0.63)	t[50]= -5.12**

SOIP: speed of information processing, MEM: memory, EF: executive functions, Global: global cognitive functioning, *: $p < .05$, **: $p < .01$.

As can be seen in **Table IV-3**, patients underperformed significantly in all four composite scores, ranging from .6 standard deviations to 1.5 standard deviations below the controls' means. Other than Global performance, the MEM composite was the most affected in my sample. The EF composite was least affected among all patients.

Table IV-4 displays the same composite scores across MS patient subgroups, again indicating significant differences to controls.

Table IV-4. *Patient subgroups' performance in composite scores.* Scores are mean z-scores (standard deviations), standardized to study controls' means.

	RR-1 (n=13)	RR-2 (n=9)	SP (n=10)	Test statistic
SOIP	-0.45 (0.60)	-1.04 (0.61)**	-1.07 (1.07)**	F[3,48]= 6.12*
MEM	-1.19 (1.23)**	-1.57 (1.36)**	-1.97 (0.76)**	F[3,48]= 9.59**
EF	-0.53 (0.85)	-0.85 (0.71)**	-0.58 (0.39)	F[3,48]= 4.30*
Global	-0.61 (0.65)**	-1.11 (0.71)**	-1.18 (0.35)**	F[3,48]= 11.46**

SOIP: speed of information processing, MEM: memory, EF: executive functions, Global: global cognitive functioning, *: $p < .05$, **: $p < .01$ in post-hoc Dunnett's t-tests comparing each subgroup to controls.

There were between-subgroup differences in all four cognitive domains, with the greatest differences in overall functioning (Global) and MEM and the least in EF. While the RR-1 group was only impaired in the Global cognitive composite score, the RR-2 subgroup was impaired in all domains. SP patients were impaired in all domains except EF. Taken together, MS patients were impaired across domains of cognitive functions, with most pronounced problems in the memory domain, followed by problems in information processing speed. Executive functions were only mildly impaired. The RR-1 subgroup showed the least impairment. The RR-2 subgroup showed most deficits, and were the only subgroup with notable executive function deficits. It should be noted that even though not all domains were impaired equally, all three patient subgroups numerically underperformed compared to controls. That is, even the least impaired RR-1 subgroup did show significant impairment when all scores were summarized in the Global cognitive composite score.

Clinically, neuropsychological test scores that are greater than or equal to two standard deviations below scores of controls indicate significant impairment. The proportion of individuals in each patient subgroup performing less than or equal to two standard deviations below the controls in each of the 4 composite scores can be seen in **Appendix C.**

3. Performance in psychosocial questionnaires

Several self-report psychosocial questionnaires were administered only to the MS patients. Since the controls were not administered these questionnaires, the MS patients' results in the psychosocial variables are reported in comparison to normative scores from test manuals or norm studies.

Hospital Anxiety and Depression Scale: In the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, [1983]), a self-report questionnaire that assesses current anxiety and depression symptoms, patients were mostly unaffected 9see **Table IV-5**). The only slight elevation was seen in the RR-2 subgroup reporting mild levels of increased anxiety.

Table IV-5. *Hospital Anxiety and Depression Scale (HADS) results in all MS patients and in patient subgroups*. Scores are means (standard deviations). The verbal descriptor of anxiety/depression severity is based on cut-off criteria from the test manual (Zigmond & Snaith, 1983).

	MS patients (n=32)	**RR-1 (n=13)**	**RR-2 (n=9)**	**SP (n=10)**
Anxiety	7.31 (3.69) Normal	6.69 (3.75) normal	8.22 (3.83) mild	7.30 (3.71) normal
Depression	5.03 (3.30) Normal	4.38 (3.64) normal	6.56 (3.24) normal	4.50 (2.68) normal

Fatigue Assessment Inventory: The Fatigue Assessment Inventory (FAI) assesses several aspects of fatigue with 4 factors (F1: overall fatigue severity ["severity"], F2: situational triggering of fatigue ["situation"], F3: psychological consequences of fatigue ["psychological"], F4: likeliness of one's fatigue to respond to rest/sleep ["sleep"]). Schwartz and colleagues (1993) provide normative scores of 37 healthy controls, and these were used as a reference here for the patients' self-reported symptoms (see **Table IV-6**).

Table IV-6. *Fatigue Assessment Inventory (FAI) results in all MS patients and patient subgroups.* Scores are mean z-scores (standard deviations) based on norms of 37 healthy controls reported in Schwartz et al. (1993).

	MS patients (n=32)	**RR-1 (n=13)**	**RR-2 (n=9)**	**SP (n=10)**
F1: Severity	2.42	2.32	2.53	2.46
	(0.86)	(0.93)	(1.07)	(0.61)
F2: Situation	0.84	0.7	0.7	1.14
	(0.54)	(0.39)	(0.62)	(0.57)
F3: Psychological	0.57	0.45	0.74	0.58
	(0.79)	(1.01)	(0.75)	(0.47)
F4: Sleep	0.18	0.17	0.05	0.41
	(1.27)	(0.97)	(1.58)	(1.41)

As can be seen in **Table IV-6**, the MS patients scored more than two standard deviations higher than healthy controls in the first factor, indicating substantial overall fatigue severity across all subgroups. Other aspects of fatigue were only slightly elevated, ranging between 0.05 and 1.14 standard deviations above controls' means. It should be noted that FAI-items summarized in factors F2-F4 represent situational, psychological, and sleep-related qualifiers of the experience of fatigue. As such, controls in the norm sample endorsed these items to a higher degree than the judgements they made about the overall severity of their fatigue. As a consequence, the patients' scores were comparable to controls among F2-F4, while being elevated in F1. Notably, the patients showed a similar increase in F1 as did MS patients reported in Schwartz et al. (1993).

Dysexecutive Questionnaire: Bodenburg and Dopslaff (2008)'s norms were used to analyze the Dysexecutive Questionnaire (DEX; self-version). Factor (F)1 measures the perceived ability to initiate and sustain ("initiate/sustain") actions in a broad sense. F2 measures perceived impulse control and sequencing ("impulse control/sequencing") of information or actions. F3 measures the individual's psychophysical and mental excitability ("excitability"). F4 measures the perceived ability to incorporate social standards into interpersonal interactions ("social"). Results are displayed in **Table IV-7.**

Table IV-7. *Dysexecutive Questionnaire (DEX) results in all MS patients and patient subgroups.* Scores are means (standard deviations). The verbal descriptor is based on cut-off scores from Bodenburg and Dopslaff (2008).

	MS patients (n=32)	RR-1 (n=13)	RR-2 (n=9)	SP (n=10)
F1: Initiate/sustain	8.00 (4.37) mild	7.46 (4.82) mild	9.78 (4.63) moderate	7.10 (3.35) mild
F2: Impulse control/sequencing	6.00 (2.92) moderate	5.69 (3.54) moderate	7.22 (2.59) moderate	5.30 (2.11) mild
F3: Excitability	3.78 (2.89) moderate	3.31 (2.25) mild	3.67 (2.78) moderate	4.50 (3.78) moderate
F4: Social	2.56 (1.98) moderate	2.00 (2.08) mild	3.11 (2.09) mild	2.80 (1.75) mild
DEX total score	20.34 (10.28) mild	18.46 (11.70) mild	23.78 (9.96) moderate	19.70 (8.71) mild

According to Bodenburg and Dopslaff's (2008) cut-off scores, the MS patients reported experiencing mild to moderate executive dysfunctions. Of note, the RR-2 subgroup reported moderate levels of dysexecutive functions in three of the four factors, while the other subgroups each reported impairments only in one of the four factors. The RR-2 subgroup was also the only subgroup that self-reported moderate levels of dysexecutive functions in the entire scale. This pattern matches well with my observation that the RR-2 subgroup also showed most pronounced impairment in objective assessments of executive functions (cf. **Tables IV-2 and IV-4**). Of note, the DEX is best used in conjunction with a collateral assessment from a caregiver or friend. These 'other' ratings can be used to contrast the patient's self-ratings, and to illustrate a possible lack of insight as part of a dysexecutive syndrome. Although I originally intended to collect such 'other'-rated questionnaires, only a small number of patients provided contact information of a relative or friend and/or the relative or friend did not provide the ratings I requested. Due to these difficulties with recruitment, I do not report on the only partially collected 'other'-rated version of the DEX here.

London Handicap Scale: For the London Handicap Scale (LHS), used to assess perceived handicap in multiple domains of daily life, Harwood and colleagues (1994) provide cut-off scores indicating levels of disability in domains mobility, physical independence, occupation, social integration, orientation, and economic

self-sufficiency. In addition, these subscale scores can be transformed into one total score, ranging between 0 and 1, with 1 reflecting no perceived handicap and 0 reflecting most severe perceived handicap. The total score is reported here, showing that the MS patients perceived themselves as being more functional than disabled (see **Table IV-8**).

Table IV-8. *London Handicap Scale (LHS) results in all MS patients and in patient subgroups.* Scores are means (standard deviations) of the LHS total score, calculated based on Harwood and colleagues (1994).

	MS patients (n=32)	**RR-1 (n=13)**	**RR-2 (n=9)**	**SP (n=10)**
LHS Total	0.69 (0.17)	0.73 (0.21)	0.63 (0.15)	0.69 (0.14)

Interestingly, LHS handicap severity did not covary with disability (EDSS) in my sample (correlation: r[30]= -.175, p > .1) and as can be seen in **Figure IV-1**, several SP patients reported rather minimal handicap in the LHS. The reason for the lack of an association between LHS and EDSS in patients is difficult to determine. Possible reasons could comprise lack of patients' insight into their own functional disability or, in contrast, effective coping abilities of patients may allow them to manage the effects of their disease relatively well. Clarification of such reasons should be sought in future studies.

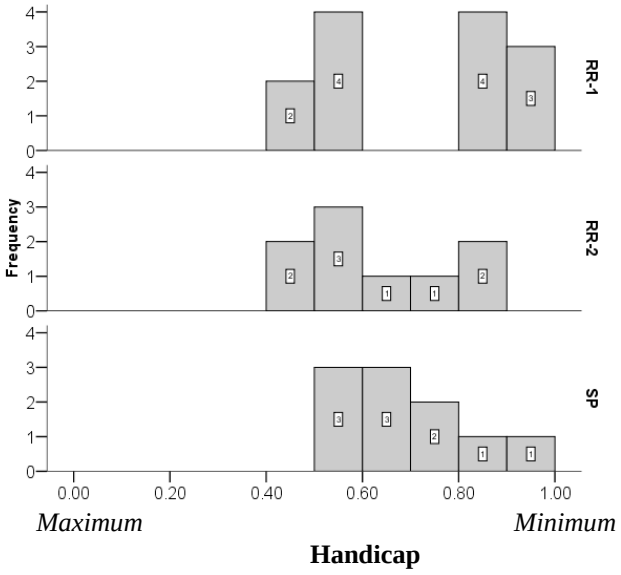

Figure IV-1. *Distribution of handicap scores across patient subgroups in the London Handicap Scale (LHS).*

4. Game of Dice Task (GDT)

4.1. GDT net-score

I first investigated whether the GDT net-score differed between patients and controls. As outlined previously, the GDT net-score is calculated by subtracting the risky decisions (1- or 2-number choices) from the safe decisions (3- or 4-number choices). Thus, GDT net-scores can range from -18 to 18, with a higher net-score indicating more safe decisions were made. Since GDT net-scores were normally distributed in patients and controls, I compared the mean GDT net-score between controls (n=20) and MS patients (n=32) using a t-test. MS patients (M= 6.81, SD= 10.85) scored lower than controls (M= 12.50, SD= 7.59), and this difference was statistically significant (t[50]= -2.05, p= .046).

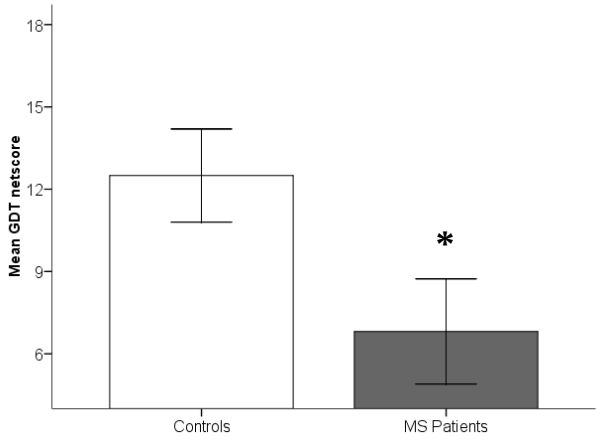

Figure IV-2. *Mean differences in GDT net-score between controls and MS patients.*
* p < .05, error bars are standard errors of the mean.

A one-way ANOVA was conducted to test between-group difference in GDT net-score between controls and MS patient subgroups (RR-1: M= 13.69, SD= 5.82; RR-2: M= 0.22, SD= 11.77 and SP: M= 3.80, SD= 10.73). Although GDT net-scores within each of the subgroups did not violate the normal distribution, I observed variance inhomogeneity across groups according to Levene's test (W[3,48]= 0.036). The Welch-test to adjust the omnibus F-effect showed significant differences in GDT net-scores among subgroups: Welch F[3, 20.527] = 4.87, p= .010. Manual post-hoc U-tests comparing each patient subgroup with the controls and adjusting for the number of comparisons (i.e.,

alpha=0.017), showed lower performance in RR-2 (U= 34.5, Z= -2.66, p= .008) and SP (U= 38.5, Z= -2.74, p= .006), but not in RR-1 (U= 127, Z= 0.114, p= .91) compared to controls. These results are illustrated in **Figure IV-3**.

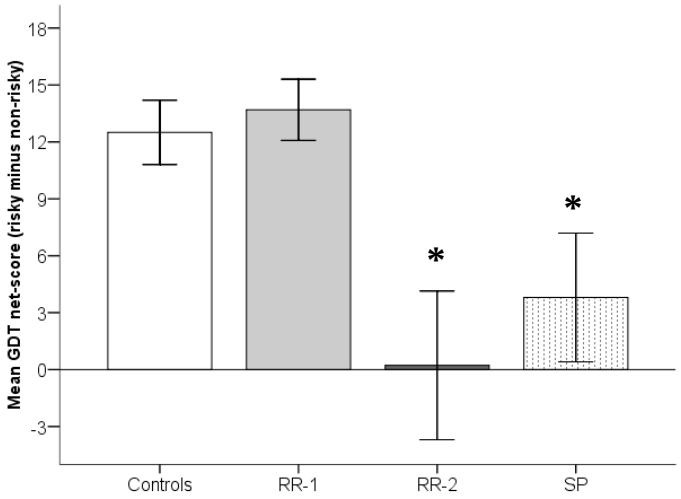

Figure IV-3. *Mean differences in GDT net-score between controls and MS patient subgroups.* * p < .05, post-hoc U-tests against controls. Error bars are standard errors of the mean.

To further illustrate this effect, I also conducted a Pearson correlation between the GDT net-score and EDSS scores (i.e., reflected in the sub-groupings). I observed a significant negative correlation, r[30]= -0.59, p<0.001, illustrated in **Figure IV-4.**

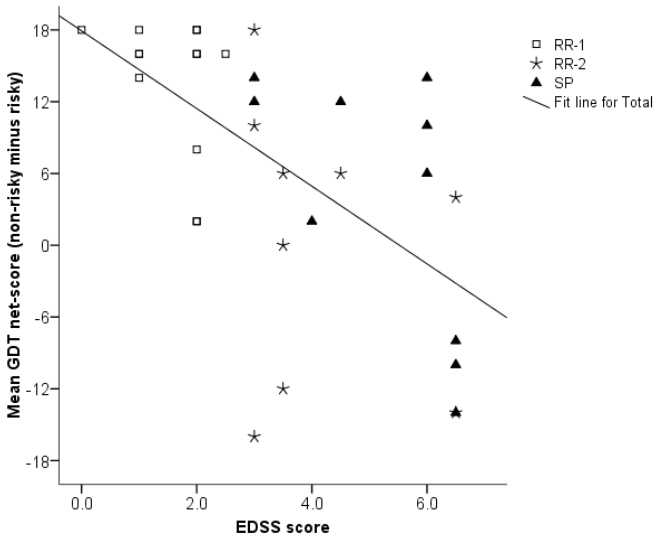

Figure IV-4. *Correlation between EDSS score and GDT net-score* (r[30]= -0.59, p< 0.001).

As can be seen in the scatter plot, the lower range of GDT net-scores was primarily made up of patients with higher EDSS scores, i.e., patients from the RR-2 and SP subgroups.

4.2. GDT: Effects of pre-morbid intelligence and years of education

Notably, the two groups with higher EDSS scores (RR-2 and SP) also had lower levels of estimated premorbid intelligence and years of education (although both differences were non-significant) and were outperformed in the GDT by the two groups with higher premorbid IQ and education (Controls and RR-1) (cf. **Table IV-10** and **Table IV-11**). I therefore wondered whether the RR-2 and SP subgroups' relative reduction in GDT performance might have been confounded by these marginal differences in the demographic variables. Note that these kinds of sampling issues are sometimes attempted to control for through analysis of covariance (ANCOVA), including variables of no interest (i.e., such as premorbid IQ/intelligence, whatever you choose or education in this case) as covariates. However, this is not a recommended practice as outlined in Miller and Chapman (2001), since, among other assumptions, ANCOVA requires the covariates and dependent variables to be correlated and the regression slopes to be homogeneous in each group. As outlined in Miller and Chapman (2001), there is no standard way to adjust such sampling biases. Moderated regression analyses, that do not impose these specific restrictions on predictors, are sometimes proposed to remedy these issues (Cohen, Cohen, Aitken, & West, 2003). I conducted two such moderated regressions to assess whether the GDT net-score differences between the subgroups were moderated by premorbid IQ or education.

The dependent variable in both analyses was the GDT net-score, the (categorical) predictor variable was subgroup, and the (continuous) moderator variable was "premorbid IQ" or "education" (years of education). I did not include both moderators together in one analysis due to problems with multicollinearity using the inter-correlated predictors premorbid IQ and education (e.g., the variance inflation factor [VIF] in a preliminary regression model including both premorbid IQ and education as moderators was VIF=5.15 for

premorbid IQ and VIF= 3.97 for years of education). **Table IV-9** shows the zero-order correlations between the GDT net-score, subgroup (coded as controls= 1, RR-1= 2, RR-2= 3, SP= 4) and premorbid IQ.

Table IV-9. *Correlations between GDT net-score, subgroup, and premorbid IQ*

	GDT net-score	**Subgroup (1=controls, 2= RR-1, 3= RR-2, 4= SP)**
GDT net-score	1	-0.43**
Estimated premorbid IQ	0.019	-0.32*

Estimated premorbid IQ based on Shipley (Zachary, R., 1986),* $p < .05$, ** $p < 0.01$

As expected, the GDT net-score and premorbid IQ were negatively correlated with increasing subgroup scores. However, GDT net-score was not correlated with premorbid IQ.

To prepare predictors for the moderated regressions, I first recoded subgroups into three dummy variables, using controls as the reference group, reflecting my main contrast of interest. These dummy-variables are hereafter named "d-RR-1", "d-RR-2", and "d-SP". The first dummy variable d-RR-1 was coded so that patients from the RR-1 subgroup received the code '1', and all other participants received a code of '0'; d-RR-2 coded patients from the RR-2 subgroup as '1' and all others as '0'; d-SP coded SP subgroup patients as '1' and all others as '0' (hence, controls were treated as the reference group and represented by a code of '0' in all three dummy variables). I then mean-centered "premorbid IQ" and "education" by subtracting the sample's mean from each participants' individual score. To build interaction terms, mean-centered premorbid IQ and mean-centered education were multiplied with the three dummy-coded variables depicting the subgroups.

All regressions were conducted in three consecutive steps. In step one, I included the moderator variable (premorbid IQ or education). In step two, the three dummy coded variables representing contrasts of the patient subgroups against controls were included. In the final step, I included the interaction terms. **Table IV-10** shows the results of three regression models including premorbid IQ, subgroup and their interactions.

Table IV-10. *Three regression models predicting GDT net-scores by premorbid IQ and subgroup.* Model 1 includes premorbid IQ only, model 2 includes premorbid IQ and subgroup, and model 3 includes premorbid IQ, subgroup, and the premorbid IQ x subgroup interaction terms.

Model	R	R Square	F Change	df1	df2	Significant F-change
1	.02(a)	.00	.02	1	50	p= .89
2	.57(b)	.33	7.6	3	47	p< .001
3	.65 (c)	.42	2.41	3	44	p= .08

(a) Predictors: Constant, premorbid IQ
(b) Predictors: Constant, premorbid IQ, RR-1, RR-2, SP
(c) Predictors: Constant, premorbid IQ, RR-1, RR-2, SP, RR-1 x PREMORBID IQ, RR-2 x PREMORBID IQ, SP x premorbid IQ
df1: degrees of freedom; df2: error degrees of freedom

As can be seen in **Table IV-10**, a significant increase in variance explanation emerged in model 2, i.e., when including premorbid IQ with the subgroup variables. A total of 57% of the variance in GDT net-scores was explained by including the subgroups as predictors in addition to premorbid IQ, compared to 2% when only including premorbid IQ as in model 1. The inclusion of the interaction terms (model 3) did not significantly increase the amount of variance explanation. **Table IV-11** shows all three models' omnibus effects, and each models' predictors with their significance.

Table IV-11. *Predictors of the three regression models including premorbid IQ, subgroup and their interactions*

Model	df1	df2	F	Sig.	Predictors	B	beta	t	Sig.
1	1	50	0.02	.89					
					premorbid IQ	0.02	.02	.14	.89
2	4	47	5.70	< .001**					
					premorbid IQ	-0.17	-.20	-1.58	.12
					RR-1	1.30	.06	.43	.67
					RR-2	-13.8	-.53	-3.86	< .001**
					SP	-10.19	-.40	-2.95	.005**
3	7	44	4.59	< .001**					
					premorbid IQ				
					RR-1	0.15	.18	.92	.36
					RR-2	2.49	.11	.81	.43
					SP	-14.43	-.55	-4.1	< .001**
					Int.: premorbid IQ x RR-1	-11.16	-.44	-3.04	.004**
					Int.: premorbid IQ x RR-2	-0.37	-.20	-1.32	.19
					Int.: premorbid IQ x SP	-0.59	-.38	-2.37	.022*
						-0.66	-.29	-1.91	.06

df1: degrees of freedom; df2: error degrees of freedom; Sig.: Significance; Int.: interaction; **: p < .01; *: p < .05

As can be seen in **Table IV-11**, both models 2 and 3 showed significant omnibus effects. Mirroring the ANOVA results (see **Figure IV-3**), RR-2 and SP, contrasted to controls, both (negatively) predicted GDT net-scores in model 2. Interestingly, model 3 found a significant interaction between premorbid IQ and subgroup RR-2 in predicting GDT net-scores, i.e., a moderating effect of premorbid IQ on GDT in this subgroup. To illustrate this interaction, participants were divided into two premorbid IQ groups based on median split (median premorbid IQ= 107.5).

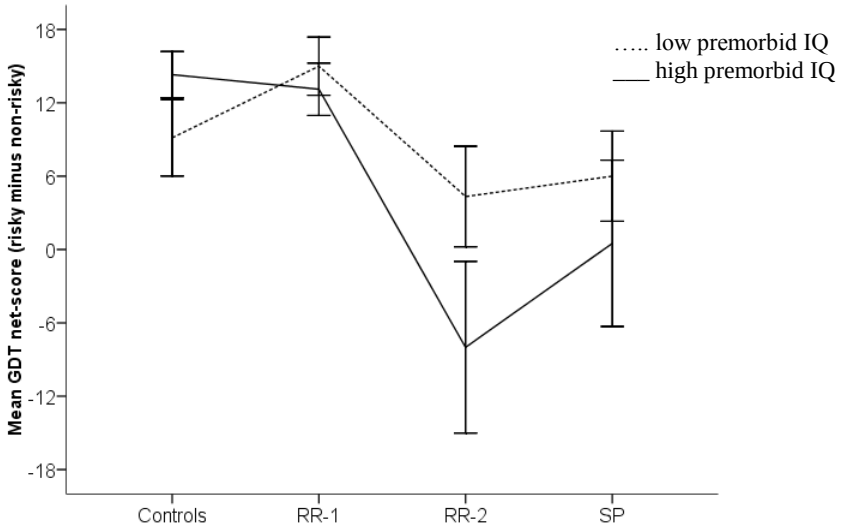

Figure IV-5. *GDT-net-scores in each subgroup separated by low and high premorbid IQ (median split).* Error bars are standard errors of the mean.

Of note, in all three patient subgroups, individuals with premorbid IQ lower than the median premorbid IQ of 107.5 performed *better* on the GDT than those with a higher premorbid IQ, with most pronounced differences in the RR-2 subgroup. Thus, most importantly, since there were pre-existing marginal differences in premorbid IQ (i.e., higher premorbid IQ in controls/RR-1 patients than in RR-2/SP patients cannot explain lowered GDT performance in RR-2 and SP). Based on the significant interaction term in model 3, if anything, RR-2 patients' lower premorbid IQ scores were related to increased GDT performance in this subgroup. Taken together, I found minimal evidence for differential moderation of GDT scores by premorbid IQ within each of the subgroups. Their

pre-existing marginal differences in premorbid IQ even favoured low-premorbid IQ RR-2 patients with regard to GDT performance. Therefore, I considered the marginal premorbid IQ-differences as unproblematic with regard to interpreting subgroup differences in the GDT net-score and retain my original interpretation: GDT was impaired in RR-2 and SP patients, irrespective of their marginally lowered premorbid IQ compared to controls.

Analogous regressions were performed using years of education as a moderator. **Table IV-12** shows the results of three regression models including education, subgroup and the interaction terms.

Table IV-12. *Three regression models predicting GDT net-scores by years of education and subgroup.* Model 1 includes education only, model 2 includes education and subgroup, and model 3 includes education, subgroup, and the education by subgroup interaction terms.

Model	R	R Square	F Change	df1	df2	Significant F-change
1	.08 (a)	.006	.32	1	50	p= .57
2	.55 (b)	.30	6.49	3	47	p< .001
3	.63 (c)	.39	2.33	3	44	p= .09

(a) Predictors: Constant, education
(b) Predictors: Constant, education, RR-1, RR-2, SP
(c) Predictors: Constant, education, RR-1, RR-2, SP, RR-1 x education, RR-2 x education, SP x education
df1: degrees of freedom; df2: error degrees of freedom

Similar to the regression models including PREMORBID IQ as a moderator, a significant increase in variance explanation emerged only in model 2, i.e., when including the dummy-coded subgroup variables along with years of education. A total of 55% of the variance in GDT net-scores was explained by including the subgroups as predictors in addition to education, compared to 8% when only including education. Again, the inclusion of the interaction terms slightly increased the amount of variance explanation, but this increase in variance explanation was not significant (63% of the variance in GDT net-scores was explained by model 3). **Table IV-13** shows all three models' omnibus effects, and each models' predictors with their significance.

Table IV-13. *Predictors of the three regression models including years of education, subgroup and their interactions.*

Model	df1	df2	F	Sig.	Predictors	B	beta	t	Sig.
1	1	50	0.32	.57					
					education	0.42	0.08	.57	.57
2	4	47	4.97	.002**					
					education	-0.45	-.09	-.66	.51
					RR-1	0.95	.04	.301	.77
					RR-2	-12.94	-.49	-3.54	<.001**
					SP	-9.31	-.37	-2.65	.011*
3	7	44	4.09	.002**					
					education	-0.53	-.10	-0.58	.56
					RR-1	0.74	.03	0.24	.81
					RR-2	-16.08	-.61	-4.33	<.001**
					SP	-7.34	-.29	-1.88	.07
					Int.: education x RR-1	1.48	.15	0.99	.33
					Int.: education x RR-2	-3.65	-.27	-1.86	.07
					Int.: education x SP	2.99	.14	0.96	.34

df1: degrees of freedom; df2: error degrees of freedom; Sig.: Significance; Int.: interaction; **: $p < .01$; *: $p < .05$

In this set of analyses, again models 2 and 3 showed significant omnibus effects. In model 2, RR-2 and SP, contrasted to controls, both (negatively) predicted GDT net-scores, similar to the analyses including PREMORBID IQ as moderator. That is, even when education was included in model 2 in a first step, subgroups RR-2 and SP showed significantly lower GDT net-scores than controls. Of note, in model 3, the reduction in GDT net-score in the SP subgroup became only a trend difference after accounting for education. The included interaction terms however, also did not significantly predict GDT net-scores. Taken together, GDT was impaired in RR-2, irrespective of their marginally lower level of education compared to controls. SP patients were only marginally impaired in the GDT when education was controlled for.

4.3. GDT performance across risk-levels

The pattern of responding in the GDT was further analyzed by inspecting the frequency of choices from each risk level across patients and controls. For this purpose, two repeated measures ANOVA were conducted with within-subject factor risk-level (1-number, 2-number, 3-number and 4-number choices) and between subject factor group (controls, all MS patients) or subgroup (controls,

RR-1, RR-2, SP), respectively. It should be noted that these models are undetermined when assessing main effects of risk level, since choices from each risk level are mutually exclusive. Thus, the main purpose of these analyses was to show potential interaction effects between group/subgroup and frequencies of choices from each of the four risk levels. The first ANOVA using group (controls vs. all MS patients) as a between-subjects factor did not show a significant interaction between risk-level and group ($F[3, 150] = 1.65$, $p > .1$). However, the second ANOVA using subgroups as a between-subjects factor showed a significant interaction between subgroup and risk level ($F[5.76, 92.14$, Greenhouse-Geisser corrected$] = 3.29$, $p < .01$). This interaction is illustrated in **Figure IV-6**.

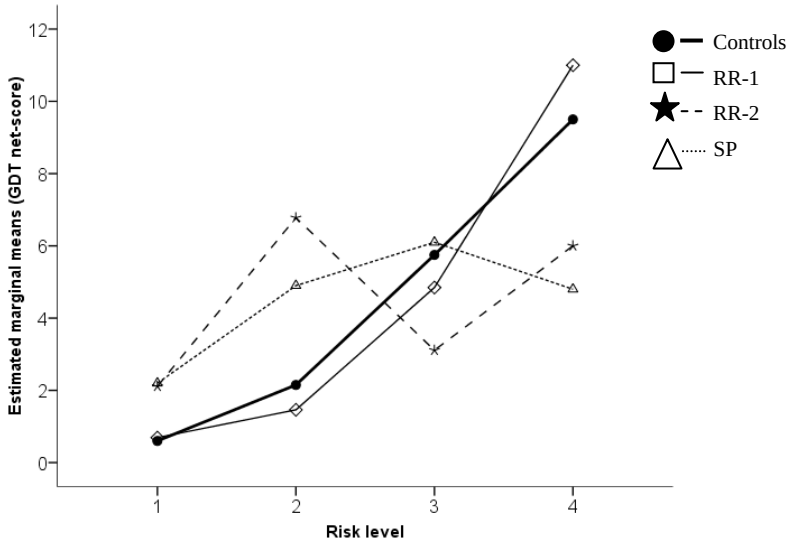

Figure IV-6. *Frequency of decisions across the four GDT risk levels.* Risk level 1=1-number choices, 2= 2-number choices, 3=3-number choices, 4=4-number choices. *: $p < .05$, t-test against controls, Bonferroni-corrected.

Inspecting **Figure IV-6**, differences between controls and RR-2 as well as SP patients were suspected, paralleling my findings with the GDT net-score. Since Dunnett t-tests were not feasible due to the undetermined main effects of risk-level, I conducted post-hoc t-tests contrasting controls against the RR-2 and the SP patient subgroup, manually correcting for the number of comparisons (eight comparisons were conducted, and therefore, alpha = .05 / 8 = 0.00625). RR-2 patients ($t[27]= 3.25$, $p= .003$) and SP patients ($t[28]= 2.39$, $p= .024$)

endorsed more 2-number choices than controls (RR-2: M= 6.78, SD= 4.76; SP: M= 4.9, SD= 3.1, controls: M=2.15, SD= 2.89). SP patients also endorsed fewer 4-number choices (SP: M= 4.8, SD= 4.8) than controls (M= 9.5, SD= 5.52; t[28]= 2.29, p= .03). Of these differences, only the RR-2 patients' increase of 2-number choices remained significant after Bonferroni-correction.

4.4. Shifting between risk levels in the GDT

One additional aspect of GDT performance patterns, shifting between risk levels, was evaluated based on a previous GDT finding in early AD patients (Delazer et al., 2007). Despite obtaining similar net-scores as controls, early AD patients made more frequent shifts between risky and safe decisions, pointing to less consistent responding and a more random choice strategy. Thus, I tested whether patients and controls in my study differed in their total number of trial-to-trial shifts between safe and risky choices. For this purpose, I calculated between-trial choice contingencies so that each choice that was followed by a different risk-level choice was counted as a shift. For example, a choice pattern of 4-2-2-1-3-4 contains two shifts (4-2[shift]-2-1-3[shift]-4). The total number of shifts was calculated over all 17 trials following trial 1. As before, analyses were carried out first comparing controls with all MS patients, and then comparing controls with each patient subgroup.

Controls and all MS patients did not significantly differ in their total number of shifts between risky and safe choices (controls: M= 2.55, SD = 3.19; MS patients: M= 4.06, SD= 3.37; t[50]= 1.61, p= .14). Comparing controls and patient subgroups with one-way ANOVA, I observed a significant between-group difference (F[3,48]= 3.55, $p < .05$). Post-hoc Dunnett t-tests showed that the RR-1 subgroup did not differ significantly from controls in their number of shifts (mean difference= -0.24, SE=1.11, $p > .05$). The RR-2 subgroup (mean difference= 2.01, SE= 1.25) had more shifts than controls, but this difference was not significant ($p > .05$). The SP subgroup (mean difference= 3.35, SE= 1.21) made significantly more shifts than controls (p= .023, see **Figure IV-7**).

This finding may imply a particularly erratic choice strategy in SP patients. In turn, the previously observed decrement in GDT performance in RR-2 patients cannot be solely attributed to random shifting of choices. One could speculate that RR-2 patients persisted or persevered in making risky choices rather than shifted randomly between risk levels.

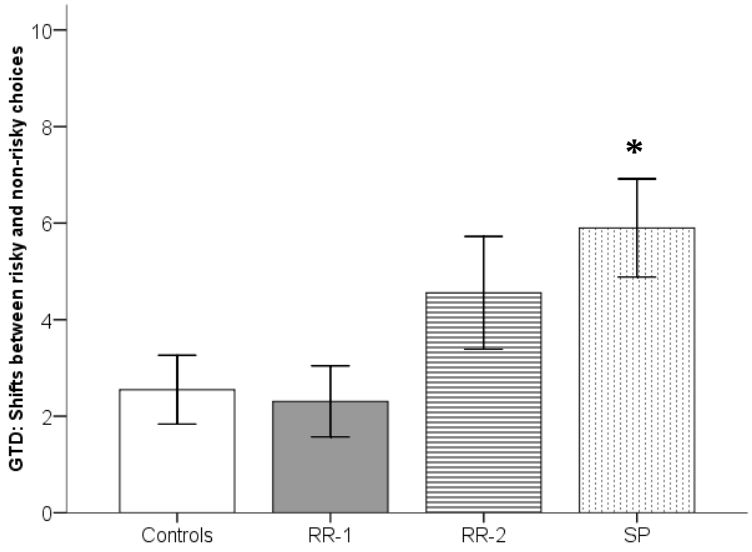

Figure IV-7. *Total number of shifts between risky (1- and 2-number choices) and safe choices (3- and 4-number choices) in the GDT.* * $p < .05$, post-hoc Dunnett t-tests against controls. Error bars are standard errors of the mean.

4.5. Perseverations on choosing the same risk levels in the GDT

To follow up on the findings in with the GDT shift scores (see **Section IV-4.6.**), I then tested whether the number of perseverations on safe or risky choices differed significantly between groups. For this purpose, I calculated trial-by-trial choice contingencies in that each choice that was followed by the same risk-level choice was counted as either a 'safe perseveration' or a 'risky perseveration'. For example, a choice pattern of 4-2-2-1-3-4 contains two risky perseverations (2-2 [risky perseveration]-1 [risky perseveration]) and one safe perseveration (3-4). The total number of such safe and risky perseverations was calculated over all 17 trials following trial 1. Furthermore, to control for the total number of safe or risky choices made during the task, the total number of perseverations was divided by the number of safe and risky choices. Thus, the maximum percentage

of risky or safe perseverations could be 94.4% (17 out of 18 safe or risky choices). Risky perseverations were non-normally distributed in controls and safe perseverations were marginally non-normal (Kolmogorov-Smirnoff Z= 1.27, p= .08). For consistency, descriptive statistics of safe/risky perseverations for controls and patients, as well as patient subgroups are shown as medians and ranges in **Table IV-14.**

Table IV-14. *Percentage of GDT safe and risky choice perseverations out of the total number of safe/risky choices.* Scores are medians and ranges.

	Controls (n=20)	**MS patients (n=32)**	**RR-1 (n=13)**	**RR-2 (n=9)**	**SP (n=10)**
Safe perseverations	92.51% (29-94%)	77.5% (0-94%)	88.24% (60-94%)	58.33% (0-94%)	72.38% (0-88%)
Risky perseverations	0% (0-86%)	16.67% (0-94%)	0% (0-63%)	50% (0-94%)	8.3% (0-92%)

As can be seen in **Table IV-14**, controls made almost entirely safe perseverations, i.e., of all safe choices they made, 92.51% were safe choices followed by another safe choice. RR-2 patients followed a safe choice with another safe choice in only 58.33% of trials. In addition, of all risky choices the RR-2 patients made, half were risky perseverations.

To formally test the two perseveration scores, I first compared controls and all patients using non-parametric U-tests for both comparisons, Bonferroni-correcting by two (i.e., the two compared scores: alpha = .05/2 = 0.025). As can be seen in **Table IV-15**, controls showed significantly more safe perseverations than all patients. The number of risky perseverations was not different. A Kruskal-Wallis non-parametric ANOVA comparing controls and patient subgroups showed significant omnibus effects for both scores (safe perseverations: χ^2 [3]= 15.61, p< .001; risky perseverations: χ^2 [3]= 9.88, p< .02). Post-hoc U-tests compared both scores in each subgroup with controls, Bonferroni-correcting for all conducted comparisons (i.e., two scores and three groups, equalling six comparisons total; alpha = .05/6 = .0083). Results of these post-hoc tests are also shown in **Table IV-15.**

Table IV-15. *Safe and risky choice perseverations in the GDT*

	MS patients (n=32)	RR-1 (n=13)	RR-2 (n=9)	SP (n=10)
Safe perseverations	U= 198.5	U= 128	U= 38.5	U= 32
	Z= -2.31	Z= -0.76	Z= -2.47	Z= -3.02
	p= .02*	p= .94	p= .014	p= .002*
Risky perseverations	U=243.5	U= 130	U= 34	U= 79.5
	Z= -1.583	Z= 0	Z= -2.85	Z= -1.04
	p= .11	p= 1	p= .004*	p= .3

*: $p < .05$, Bonferroni-corrected

As suspected based on results using the shift scores, RR-2 patients perseverated significantly more on risky choices than controls (whose median risky perseveration score was zero). In addition, SP patients did not show more risky perseverations than controls, but perseverated significantly less on safe choices. This is partly mirrored in my previous finding of increased shifting in (only) the SP patients compared to controls.

5. GDT correlations with neuropsychological measures

Apart from the already reported correlation between GDT net-score and EDSS (see **Figure IV-4**), risky and safe perseverations in the GDT were also correlated with EDSS (risky perseverations: rho [30] = .45, $p < .05$; safe perseverations: rho [30] = -.67, $p < .001$), indicating more risky perseverations and fewer safe perseverations in the GDT with increasing MS-related disability. None of the demographics (age, sex, premorbid IQ, years of education [tested with Pearson correlations]) or disease-related variables (duration of MS, age at onset of MS, tested with partial correlations controlling for age) were correlated with the GDT net-score, number of shifts, and risky or safe perseverations in either controls or MS-patients.

Next, correlations between the GDT net-score, GDT total number of shifts and cognitive composite scores were investigated[1]. Pearson correlations were used to test relationships within larger samples (controls, all MS patients) and

[1] Note that I also tested relationships between cognition and GDT risky/safe perseverations. These were all non-significant and are not further reported here.

Spearman rank correlations were used to test relationships within the smaller sized patient subgroups. Results are shown in **Table IV-16**.

Table IV-16. *Correlations between GDT net-score /total number of shifts and the cognitive composite scores.* Pearson r was used in controls and all patients; Spearman rho was used within patient subgroups.

	Controls (n=20)	**All MS patients (n=32)**	**RR-1 (n=13)**	**RR-2 (n=9)**	**SP (n=10)**
SOIP	-.15 / -.05	.41* / -.02	.13 / .09	.01 / -.50	.39 / .37
MEM	.25 / -.17	-.06 / -.31	-.53 / .43	.05 / -.77*	.17 / -.23
EF	.18 / -.22	.22 / -.08	.27 / -.39	.64† / -.30	.06 / .44
Global	.17/ -.18	.25 / -.20	.19 / -.01	.13 / -.72*	.33 / .47

SOIP: speed of information processing, MEM: memory, EF: executive functions, Global: global cognitive functioning, * $p < .05$, †: $p < .1$

As can be seen in **Table IV-16**, there was a significant positive correlation ($r[30]= 0.41$, $p < .05$) between the information processing speed (SOIP) composite score and the GDT net-score in all MS patients. In controls, none of the composite scores significantly correlated with GDT net-score. In patient subgroups, GDT net-score did not significantly correlate with any of the composite scores. It should not noted that, within the RR-2 subgroup only, the GDT net-score had a trend correlation ($rho[7] =.64$, $p=.06$) with the EF composite. Also, in this group only, the total number of shifts was significantly negatively correlated with MEM and Global composite scores. Taken together, I could not observe strong relationships between executive (dys-)functions and impairment in the GDT in all patients or patient subgroups, as suggested in hypothesis 2. Instead, GDT net-score covaried with information processing speed. The shift score was largely unrelated to cognition, except within the RR-2 group. In this subgroup, overall cognitive performance (especially memory) was inversely related to shifting in the GDT.

Nevertheless, I had strong reasons to hypothesize a positive correlation between executive functions and GDT at least in some patients. These are summarized in the following: a) A large body of previous research linked executive functions to GDT performance, both in healthy controls and in various

patient populations, b) there was a trend correlation between GDT net-score and EF within the RR-2 group, c) the RR-2 group was the only one of the subgroups that showed significant reductions in the EF composite score compared to controls, and d) the RR-2 group reported most dysexecutive functions in the DEX questionnaire. I therefore selectively followed up on the trend correlation between EF and GDT net-score in RR-2 patients only. For this purpose, I separated the six measures contributing to the EF composite score and tested which one of them was correlated most to the GDT net-score. Note that time/error scores were inverted, so that all correlations in **Table IV-17** are positively keyed. The alpha-level for these correlations was adjusted by a factor of 6 (alpha =.05 / 6 = .0083) to account for the number of comparisons. The results of these correlations are shown in **Table IV-17.**

Table IV-17. *Correlations between GDT net-score and single measures within the EF composite score in RR-2 patients only.* Scores are Spearman rank correlations.

Test score	Correlation with GDT net-score
SRT Intrusions	.15
TOH (Time)	-.34
WCST Total Correct	. 82*
WCST Perseverative Errors	.24
COWAT	.35
DSB	.59

*: $p < .05$, Bonferroni-corrected. SRT: selective reminding test, TOH: tower of Hanoi, WCST: Wisconsin card sorting test (64-card version), COWAT: verbal fluency test, DSB: digit span backward.

As can be seen from the table, all tests except the time to complete the Tower of Hanoi[2] correlated positively with the GDT net-score, but only the WCST total number of correct sorts showed a significant correlation. This correlation is illustrated in **Figure IV-8**.

[2]Since not all patients completed all 3 trials in the TOH (i.e., 3-disk, 4-disk and 5-disk version), the number of trials to complete the full task could not be calculated. The proportion of patients who did not successfully complete all versions in the RR-1 subgroup was 38.5% (n=5), 44.4% (n=4) for the RR-2 subgroup and 70% (n=7) for the SP subgroup; therefore, data from these patients would have had to be excluded in my more conventional TOH analyses. As a way to preserve as much data as possible, the maximum amount of time allotted to complete each trial (300 sec) was included in these instances where no data was available. The inclusion of such artificial TOH time scores may have led to a bias in the EF composite score. A new EF composite score was recalculated with the removal of the TOH average time. The recalculated EF composite score produced similar results as the original EF composite score in all my analyses, with the only notable change that the SP group was now impaired in the new EF composite score. I decided to continue to include the (estimated) TOH time in the EF composite score to retain some representation of all executive function tests that were administered my in this study.

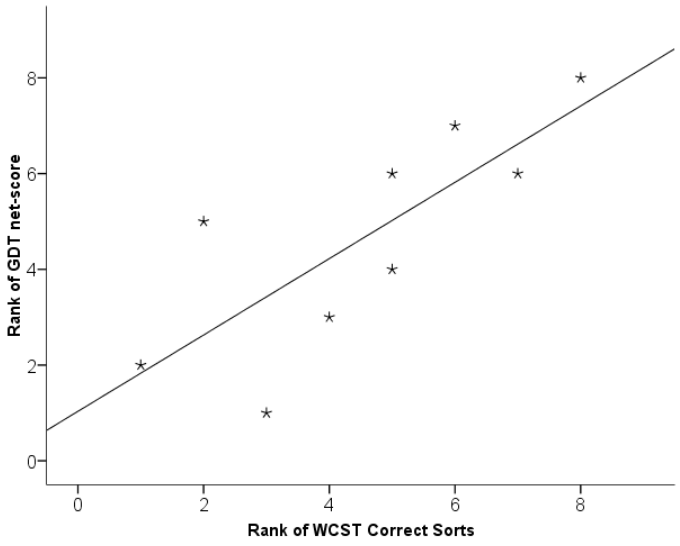

Figure IV-8. *Rank correlation between GDT net-score and correct sorts in the Wisconsin Card Sorting Test (WCST 64-card version) in RR-2 patients*

Taken together, I observed some evidence of a relationship between GDT performance and executive functions as measured with the WCST in the RR-2 subgroup, addressing hypothesis 2.

Finally, within all MS patients or patient subgroups, none of the psychosocial questionnaire measures were significantly correlated with GDT net-score, apart from one trend correlation with DEX factor 1("Ability to sustain and initiate actions") in the RR-2 subgroup (rho[7]= .62, p = 0.07). Also in the RR-2 group only, the GDT shift score was significantly related to perceived handicap in the LHS questionnaire (rho[7] = -.73, p= .025). This finding implies that RR-2 patients with more perceived handicap (closer to scoring '0' in the LHS) made more shifts in the GDT.

6. Atrophy measures

In the following section, the four linear measures of brain atrophic changes and ventricular width (Frontal horn width= FHW; Intercaudate distance= ICD; Third ventricle width= TVW; Intercaudate Ratio= ICR) are described. Note that imaging data of one patient from the RR-1 subgroup was not available. **Table IV-18** illustrates comparisons between MS patients' linear atrophy measures and

those acquired from control patients' MR scans. Of note, TVW was non-normally distributed in control patients and could not be remedied by log-transformation; therefore, non-parametric U-test was used to compare TVW between MS patients and control patients.

Table IV-18. *Linear atrophy measures in MS patients and control patients.* Scores are means (standard deviations) or median (ranges) in centimetres

	Control patients (n=20)	All MS patients (n=31)	Test statistic
FHW	3.18 (0.38)	3.26 (0.28)	T[49]= 0.4
ICD	1.04 (0.24)	1.22 (0.27)	T[49]= 2.48*
ICR	0.09 (0.02)	0.11 (0.02)	T[49]= 2.83**
TVW	Md.: 0.17 (Rg.: 0.11- 0.7)	Md.: 0.23 (Rg.: 0.1- 1.0)	U= 198.5 Z= -2.31*

*: p < .05; **: p < .01; FHW: Frontal Horn Width; ICD: Intercaudate distance; ICR: Intercaudate ratio; Md.: Median; Rg.: Range; TVW: Third ventricle width.

As can be seen in **Table IV-18**, all MS-patients as a group had significantly larger ICD, ICR and TVW than control patients. In addition, I also compared MS-patient subgroups' atrophy measures to those of the control patients. These comparisons are shown in **Table IV-19**.

Table IV-19. *Linear atrophy measures in MS patient subgroups and control patients.* Scores are means (standard deviations) or median (ranges) in centimetres

	Control patients (n=20)	RR-1 (n=12)	RR-2 (n=9)	SP (n=10)	Test statistic
FHW	3.18 (0.38)	3.33 (0.32)	3.16 (0.31)	3.28 (0.19)	F[3,47]= 0.73
ICD	1.04 (0.24)	1.17 (0.25)	1.25 (0.33)	1.26 (0.25)	F[3,47]= 2.33†
ICR	0.09 (0.02)	0.10 (0.02)	0.11*[1] (0.03)	0.11*[1] (0.02)	F[3,47]= 3.67*
TVW	Md.: 0.17 (Rg.: 0.11- 0.7)	Md.: 0.20 (Rg.: 0.1- 1.0)	Md.: 0.25 (Rg.: 0.13- 0.84)	Md.: 0.23 (Rg.: 0.14- 0.92)	χ^2 [3]= 5.79

[1]: Post-hoc tests were Dunnett t-tests against control patients; *: p < .05; †= p <.1; FHW: Frontal Horn Width; ICD: Intercaudate distance; ICR: Intercaudate ratio; TVW: Third ventricle width.

As can be seen in **Table IV-19**, MS-patient subgroups statistically differed from control patients in the ICR measure and showed a trend difference in ICD. Both RR-2 and SP patients had significantly larger ICRs than control patients. TVW was not significantly different across subgroups (p= .12).

Taken together, these results corroborate the usefulness of these linear atrophy measures to delineate differences between MS patients and non-MS individuals. There seemed to have been a particular sensitivity of measures approximating basal ganglia atrophy (ICR/ICD) here, and less pronouncedly so, thalamic atrophy (TVW). Frontal horn width was insensitive to MS-status or MS-subgroup.

6.1. Correlations between atrophy measures and disease-related parameters

To further validate these scores' utility, I conducted partial correlations controlling for age and sex between the atrophy measures and the disease-related parameters disease duration, age at MS onset, and EDSS. Age was controlled to account for the patients' middle-age range (mean = 50.81 years of age), i.e., an age when brain changes can be observed even in healthy aging individuals (e.g., Raz & Lindenberger, 2010; Salonen, Autti, Raininko, Ylikoski, & Erkinjuntti, 1997). Sex was controlled to account for smaller brain sizes in females than males. To retain statistical power with reduced degrees of freedom due to partial correlations, and given that (some) of the measures were sensitive to MS subgroup status, MS patients were collapsed into one group and no further analyses per MS-patient subgroup were conducted. Since TVW was normally distributed in MS patients, Pearson partial correlations were conducted for all four linear atrophy measures. The results of these partial correlations are presented in **Table IV-20**.

Table IV-20. *Partial correlations in MS patients, controlling for age and sex, between the linear brain atrophy measures and disease parameters*

	FHW	ICD	ICR	TVW
Age at onset of MS	-.18	-.21	-.22	-.32†
MS duration	.24	.30	.31	.38*
EDSS	-.10	.24	.36†	.20

*= $p < .05$; †= $p < .1$; FHW: Frontal Horn Width; ICD: Intercaudate distance; ICR: Intercaudate ratio; TVW: Third ventricle width; EDSS: Expanded Disability Status Scale

Controlling for age and sex, a longer MS duration was significantly correlated with increased TVW. A similar trend was found for a younger age at onset of MS. EDSS showed a trend correlation (p= .057) with the size of the ICR. Thus, the partial correlations further support that the linear atrophy measures are tracking brain changes associated with progression and severity of MS. Next, I present correlations between atrophy and cognition in MS patients.

6.2. Correlations between atrophy measures, cognition, and GDT

I tested whether the four linear atrophy measures were correlated with MS patients' (n=31) performance on the four cognitive composite scores as well as the GDT measures net-score and total number of shifts, again controlling for age and sex. Results of these partial correlations are given in **Table IV-21**.

Table IV-21. *Partial correlations, controlling for age and sex, between the linear brain atrophy measures and cognitive composite scores, GDT net-score and GDT number of shifts in MS patients*

	FHW	ICD	ICR	TVW
SOIP	.02	-.51**	-.57**	-.54**
MEM	.12	-.01	-.07	-.12
EF	.16	-.05	-.10	.06
Global	.16	-.21	-.29	-.21
GDT net-score	.18	-.39*	-.48*	-.47*
GDT shifts	-.18	-.21	-.14	-.05

** p < .01* p < .05; FHW: Frontal Horn Width; ICD: Intercaudate distance; ICR: Intercaudate ratio; TVW: Third ventricle width; SOIP: Speed of Information Processing composite score; MEM: memory composite score; EF: Executive function composite score; Global: Global cognitive composite score

Controlling for the effects of age and sex, ICD, ICR and TVW were significantly negatively correlated with the SOIP composite score. GDT net-score and atrophy measures showed similar, but weaker relationships. Of note, the GDT shift score was unrelated to any of the atrophy measures and neither of the GDT scores or cognitive composite scores correlated with FHW. Note that partial correlations between GDT net-score and atrophy, controlling for SOIP in addition to age and sex, reduced but did not eliminate some of the previously significant

partial correlations (ICD r_{part} = -.24, p>.1; ICR r_{part} = - .34, p= .08; TVW r_{part}= -.33, p= .09). That is, even though much of the atrophy-GDT relationships were likely mediated through elements of processing speed inherent in the GDT performance in the MS patients here, other aspects of the GDT may also have covaried with atrophy, albeit to a lesser extent.

V. DISCUSSION

Our study is the first to investigate decision making abilities in MS patients using the Game of Dice Task (GDT) as a measure of decision making under risk. GDT performance has been associated with executive dysfunctions in populations other than MS. I found impairment in GDT performance in 32 MS patients compared to 20 healthy controls. Deficits were confined to two subgroups of patients with more advanced disability and either RR (N=9, RR-2-group) or SP (N=10, SP group) MS subtype. Conversely, a subgroup of mildly disabled and largely cognitively intact patients with RRMS (N=13, RR-1 group) was unimpaired in decision making. Only the subgroup of moderately impaired RR-2 patients showed the expected relationship between decision making and executive functions, while decision making in the entire patient group was correlated with information processing speed. Brain atrophy was studied with four linear measurements on patients' clinical MR images and was compared with those from control patient MR images. Atrophy measures in the vicinity of the basal ganglia and thalamus (ICD, ICR, TVW) significantly differed between MS and control patients. These measures also showed negative correlations with processing speed, but none of the other cognitive composite scores. GDT performance showed the same pattern, although in a weaker form.

Thus, decision making with explicit rules as assessed with the GDT is impaired in MS patients, but only in more disabled patients. Deficits in information processing speed more consistently characterised patients' decision making impairment than executive dysfunctions. Problems with decision making and information processing speed shared increased ICD, ICR and TVW as neurological markers. In the following I will discuss these findings in more detail.

1. Impairment in the Game of Dice Task in MS

In agreement with my first hypothesis, I found decision making under risk in the GDT impaired in my sample of MS patients. This deficit was correlated with MS-related disability (EDSS). Indeed, *only* patients with more advanced disease stages (RRMS with an EDSS score of 3.0 and above; SP patients) showed

the impairment, while patients with less disability did not (RRMS with an EDSS score lower than 3.0).

1.1. Comparison with previous IGT findings in MS

Five out of six published studies investigating decision making in MS patients have used the IGT, a task designed to assess decision making under ambiguity. In four of the five IGT studies, MS patients demonstrated some form of impairment compared to controls either as slower acquisition of decision contingencies (learning slope: [Kleeberg et al., 2004]; learning index: [Simioni et al., 2008; Simioni et al., 2009]), reduced net-scores in the entire task [Nagy et al., 2006] or in the last task block [Roca et al., 2008]). Four of these studies involved relatively homogeneous groups of mild and/or early stage MS patients (EDSS: 0-3.5, disease duration: 2-4 years) and only included the RRMS subtype (Nagy et al., 2006; Roca et al., 2008; Simioni et al., 2008; Simioni et al., 2009), mainly to explore whether IGT decision making deficits could serve as an early disease (or cognitive/emotional) marker. As a result, correlations between IGT and EDSS were either not explored (Nagy et al., 2006; Roca et al., 2008) or not found (Simioni et al., 2008; Simioni et al., 2009).

Although Simioni et al. (2008) did not find CIS and very early-stage MS patients impaired in the IGT (EDSS: 1.74, disease duration: 2.1 years), both Nagy (2006) and Roca (2008) reported reduced IGT net-scores in patients with mild (EDSS: 1.7; [Nagy et al., 2006] and 0 - 1.5 [Roca et al., 2008], respectively) and slightly longer lasting, but still early-stage MS (disease duration: 3.1 years; [Nagy et al., 2006] and 2.5 years [Roca et al., 2008], respectively). Both studies found IGT net-score reductions predominantly (Nagy et al., 2006) or exclusively (Roca et al., 2008) in the last task blocks. In the last blocks of the IGT, the decision contingencies should have been acquired and are likely explicitly known by the participant. Hence, the last IGT task blocks also measure cognitive/executive aspects of decision making and are therefore most similar to tasks of decision making under risk. As such, Brand et al. (2007) showed in healthy controls that performance in the GDT is correlated with executive functions and with

performance in the last IGT blocks only. Thus, given Nagy et al.'s (2006) and Roca et al.'s (2008) results with early-stage MS, it may seem surprising that my RR-1 MS patients were entirely unimpaired in the GDT.

Note that my RR-1 group had a similarly low EDSS score (mean EDSS=1.58) compared to all three of these studies' samples. However, their disease duration was decidedly longer with an average of 17.16 years (± 12.76 years). In line with their intact GDT performance, my RR-1 group was also largely cognitively unimpaired otherwise. Thus, my RR-1 group may have consisted of a group of patients with a benign form of MS. The exact criteria for such "benign MS" are still debated, but many studies have reported the existence of a group of MS patients with a relatively favourable disease progression (few relapses, minor motor and cognitive problems over many years with little signs of deterioration) (Ramsaransing & De Keyser, 2006). Calabrese and others (2013) recently performed a direct comparison of MRI pathology of "early-stage mild RRMS patients" with so-called "benign MS patients" (low EDSS but long disease duration) in a longitudinal design. They found that benign MS patients had substantially lower cortical lesion volumes and less cortical thinning than early-stage RRMS patients. The progression of either cortical pathology was also less pronounced in benign MS. Thus, the extent of MS-related cortical pathology might play a role in the development of benign (less impaired) forms of MS. However, there are also many reports regarding the existence of subtle cognitive/behavioural problems as well as neuropathology even in "benign MS" (Amato, Portaccio, et al., 2008; Amato et al., 2006; Bester et al., 2013; Mesaros et al., 2009; Rovaris, M., Riccitelli, et al., 2008; Sayao, Bueno, Devonshire, & Tremlett, 2011) and I do need to emphasize that the RR-1 group was largely, but not entirely cognitively intact. Therefore, my RR-1 group was likely composed of both early-stage mild RRMS as well as benign, long-term MS patients and is not directly comparable to the three early-stage RRMS samples reported in Nagy et al. (2006), Roca et al. (2008), and Simioni et al. (2008). It should also be noted here that even though the positive findings in Nagy and Roca in early stage/mildly disabled RRMS patients may suggest that subtle changes in emotional reactivity

early on in MS perhaps induce problems with (emotional forms of) decision making, the IGT has been quite vehemently criticized for its low specificity (Brand, Recknor, et al., 2007; Clark, L., Manes, Antoun, Sahakian, & Robbins, 2003; Fellows & Farah, 2005; Manes et al., 2002). That is, healthy controls can show reductions in the IGT due to a number of non-pathological factors including a lack of motivation to perform the task, non-pathological impulsivity (or other personality traits), and a preference to avoid frequent losses instead of optimizing the choice strategy to maximize long-term outcomes (and, as intended, to learn choosing decks C and D over A and B) (Buelow & Suhr, 2009; Dunn, Dalgleish, & Lawrence, 2006b; Fernie & Tunney, 2006; Lin, C. H., Chiu, Lee, & Hsieh, 2007; Lin, C. H., Song, Lin, & Chiu, 2012; Maia & McClelland, 2004). Thus, impairment in the IGT, although observed in many neurological and psychiatric conditions, cannot unequivocally be interpreted as pathological. This in turn implies that reported IGT deficits in some studies with relatively early-stage MS patients (Nagy et al., 2006; Roca et al., 2008) may not be due to MS per se, but could also be caused by non-pathological factors such as depression (Simioni et al., 2008), for example, or the ones listed above. This possibility seems even more likely considering the general lack of correlations between IGT performance and other types of cognitive deficits as well as brain correlates and will be further discussed below.

The IGT study by Kleeberg et al. (2004) used a sample most similar to the current, with both RR and SP subtypes, a wide range of disease duration (0.6-25 years) and EDSS scores up to 6.5. They also stratified patients into low (≤2) and high (>2) EDSS groups, similar to my approach (≤2.5 for low EDSS and >2.5 for high EDSS groups here). In their study, IGT was correlated with EDSS, and high EDSS scorers were more profoundly impaired in the IGT, and this directly mirrors my findings with the GDT.

1.2. Comparison with Simioni et al. (2012)

A single recent study by Simioni and others (2012) investigated decision making under risk in MS patients using two other paradigms, the CGT and the

WOF task. This study found slight impairments in both tasks, again in relatively mild RRMS (mean EDSS= 1.9, disease duration: 5.06 ± 3.3 yrs). As described in more detail in the introduction, the main variables of interest in the WOF task are decision strategy changes due to the induction of emotional states of disappointment or regret, and the development of risk aversion based on past feedback. The MS patients in Simioni et al. (2012) failed to modulate their choices in anticipation of disappointment, reported less negative affect after decisions inducing disappointment or regret, but showed intact physiological responses to those trials and developed an even stronger risk aversion than controls. Thus, subtle changes in the subjective judgment and anticipation of emotional states induced slight alterations in these patients' choice behaviour. Of note, patients did not show exaggerated risk taking in the form of reduced risk aversion in their choices, something that has been reported in patients with OFC damage (Camille et al., 2004), but rather showed an *exaggerated* risk aversion. The WOF task focuses on assessing the anticipated emotions resulting from current decision outcomes on future choices and therefore is quite different from the GDT, although the WOF also provides explicit decision rules (and hence measures decision making under risk). Thus, I cannot know for certain what types of emotions were elicited by the choice outcomes in the GDT in the patients. Conceptually, the GDT provides a 'complete information' situation: Participants are given information about the actual outcomes of each die roll in every trial. To further stay within the WOF framework, such situations could potentially induce regret ("what could have been if I had made a different choice…"), an emotion that may have been blunted also in RR-2 and SP MS patients here, although this remains speculative.

The CGT is more closely aligned with the GDT and also assesses decision making under risk. The main differences between the CGT and the GDT are the CGT's timed outcome variable 'decision deliberation time' (versus the untimed GDT version here). Furthermore, participants do not need to generate long-term decision strategies in the CGT since decisions are based on winning probabilities that change in each trial. The most definitive marker of decision making

impairment in the CGT is a decrease in the number of trials before reaching bankruptcy, i.e., the time when the point capital given in the beginning of the task is spent due to disadvantageous decisions. Simioni and colleagues' patients had longer deliberation times as well as fewer choices of the most favourable odds (similar to the four-number choices in the GDT). However, their overall performance was not lowered nor did they terminate the task earlier. Thus, even though Simioni and others' findings showed that there might be slight alterations in mild RRMS patients' perceptions of emotional states in the context of feedback after decisions in the WOF, these were unaccompanied by changes in physiological responses and did not cause excessive risk taking. Slowing of decision times in the CGT was not accompanied by deterioration of decision performance per se either. My sample had higher levels of disability (all MS patients' mean EDSS= 3.4 ± 1.98), decidedly longer disease duration (15.89 ± 10.33 years) and EDSS was substantially correlated with GDT performance. Thus, taking Simioni and colleagues' results together with mine, I would argue that mild forms of MS are indeed not substantially affected in decision making under risk.

1.3. Influence of education and premorbid IQ on GDT performance

One potentially protective factor with regard to cognitive functions in the course of neurodegenerative processes is premorbid intelligence/education level ("cognitive reserve capacity") (Stern, 2002). In brief, the term "cognitive reserve" refers to situations when pre-morbidly acquired alternate cognitive strategies or other cognitive resources allow an individual to maintain high performance levels and resilience to neuropathological damage. Thus, in individuals with a high cognitive reserve, the ability to optimize or maximize performance through differential recruitment of alternative brain networks or cognitive strategies is maintained. Premorbid education levels or premorbid IQ estimates are often used to approximate a measure of such cognitive reserve. The RR-1 group had about ten more premorbid IQ points than the other two patient groups and was also educated about a year longer, even though these differences did not reach

significance. Thus, a higher "cognitive reserve" could reasonably be assumed to have driven the non-significant GDT findings in this subgroup.

However, I found no correlations between education/ premorbid IQ and GDT performance in any of the subgroups. Additionally, results from moderated regression analyses demonstrated that even when I accounted for the possible influences of premorbid IQ, the RR-2 and SP subgroups still differed significantly from controls in their GDT net-scores, and the RR-1 subgroup was still not different. Of note here, if anything, the RR-2 subgroup showed a reverse relationship between GDT performance and premorbid IQ in that RR-2 patients with a higher premorbid IQ performed worse than those with a lower premorbid IQ. With regard to education, I did find that the results from the SP group were influenced slightly by their lower education, insofar as their reductions in GDT net-scores became a trend effect after controlling for levels of education. However, GDT performance in the RR-1 group was not influenced by education levels.

Studies using the GDT to investigate decision making in other populations, such as Korsakoff Syndrome (Brand, Fujiwara, et al., 2005), mild AD (Delazer et al., 2007), binge eating disorder (Svaldi et al., 2010) and ADHD (Matthies, Philipsen, & Svaldi, 2012), have found the GDT to be uncorrelated with levels of education and many GDT studies have also found no significant correlations between the net-score and intelligence (Brand, Franke-Sievert, et al., 2007; Brand, Fujiwara, et al., 2005; Brand, Kalbe, et al., 2005; Brand, Labudda, et al., 2004). Two studies (Brand et al., 2008 & 2009) pointed to relationships between premorbid IQ estimates and GDT measures other than the net-score. Of note, a subtest from a German intelligence test battery ("LPS-4" from the Leistungsprüfsystem; Horn et al. (1983) has been used as an premorbid IQ-estimate in many of the studies by Brand's group. The LPS-4 measures logical thinking/problem solving ability and requires subjects to identify a rule in a series of digits and letters and to indicate the one that violates the rule (e.g., 111-8643-B-920-386-189, where 'B' would be the only letter and correct answer). As such, the LPS-4 measures fluid rather than crystallized/premorbid intelligence as was

assessed in the current study with the verbal subtest of the SILS. Fluid intelligence is highly correlated with age, executive functions, processing speed, and other timed tasks, while crystallized intelligence relies on (life-time) accumulated knowledge and long-term memory (Cattell, 1963). Brand et al. (2008) found that healthy participants' ability to benefit from feedback in the GDT was moderated by fluid intelligence. Similarly, Brand et al. (2009) found a negative relationship between choosing the riskiest (1-number) option in the GDT and fluid intelligence in healthy participants. Although I did not test for all of these relationships, neither net-score, number of shifts, or safe/risky perseverations were correlated with premorbid IQ within controls, all MS-patients, or patient subgroups here, likely because my premorbid IQ measure focused on crystallized (i.e., premorbid) rather than fluid intelligence. It should be noted here that relationships between GDT and age have also been found previously. The largest-scale GDT study in healthy participants across age ranges (N= 538, 18-80 years of age [Brand & Schiebener, 2013]) documented that increasing age will lead to reductions in GDT performance, but only in individuals with lower fluid intelligence levels and in those with lower executive functions. I did not find relationships between GDT and age in my sample, perhaps due to my relatively narrow age range.

An interesting finding bearing some relevance to the somewhat counterintuitive influence of premorbid IQ on GDT performance in the RR-2 group comes from Evans and others (2004). They reported an inverse relationship between education levels and performance in the IGT. In this study, healthy participants with a tertiary education level were outperformed by individuals who had a high-school education and a 14-point lower premorbid IQ in the National Adult Reading Test. However, their sample was quite small, young (<25 years of age), and female only, therefore complicating the interpretation of this finding. Furthermore, there has also been evidence to the contrary, indicating weak but *positive* relationships between education/ premorbid IQ levels and IGT performance (Davis et al.). As the RR-2 sample itself was already quite small with only 9 patients, comparison of high- and low- premorbid IQ RR-2 patients

was not pursued further here. Instead, the main reason for the moderated regression analyses was to show that GDT net-scores remained lowered in RR-2 and SP subgroups, when accounting for their marginally lower education and premorbid IQ levels; this was the case for the RR-2 group, and largely also for the SP group.

1.4. Patterns of GDT impairment in RR-2 and SP patients

Although both RR-2 and SP subgroups demonstrated GDT deficits with regard to overall net-scores (qualified by education levels in SPMS patients), their trial-by-trial performance patterns differed. Compared to controls, the RR-2 subgroup perseverated substantially more on risky choices, whereas the SP subgroup made more frequent shifts between risky and safe decisions.

Shifting decisions between risk levels has been studied in other populations with the GDT. For example, early AD patients (Delazer et al., 2007) with similar net-scores to those of healthy controls were found to make more frequent shifts between risky and safe choices, suggesting that they might be impaired in the development of a consistent decision strategy and more randomness in their choices. I found a similar pattern in the SP group, who showed significantly more shifting between choices, and their safe choices were followed less often by another safe choice, indicating a more random choice behaviour in this subgroup than in the other groups. As the number of shifts in this subgroup was not correlated with other disease-related parameters or cognitive dysfunctions, it is not clear what caused the randomness in their choices. My finding that education did influence GDT net-scores in SP patients only, one may speculate that SP patients perhaps could have optimized their erratic choice strategy with more explicit explanation of the GDT choice probabilities and/or being offered additional trials in the task.

Interestingly, RR-2 patients did not exhibit significantly higher rates of shifting, but instead they perseverated more on risky choices. In fact, RR-2 patients were the only group showing an increased frequency in choosing 2-number combinations, i.e., the second riskiest choice. Previous studies with the

GDT often selectively analyzed 1-number (riskiest) choice frequencies in various patient groups (e.g., Brand, Fujiwara, et al., 2005; Brand, Kalbe, et al., 2005; Brand, Labudda, et al., 2004; Brand, Roth-Bauer, et al., 2008; Brand & Schiebener, 2013; Svaldi et al., 2010). Choosing a single number in this task implies a fundamental misunderstanding of the probabilities and a willingness to risk the highest amount of money in the decision trial. I could not find such exaggerated endorsement of single number choices here, but instead increased 2-number combination choices in the RR-2 group. Together with their increased perseveration on risky choices (i.e., 1- and 2-number choices collapsed), the RR-2 group may have misinterpreted 2-number combinations as non-risky choices and therefore had continued to endorse these throughout the task. Again this remains speculative.

2. Correlations with GDT performance

GDT performance was related to information processing speed (SOIP composite score), and not executive functions, in my entire patient sample. However, GDT performance was marginally related to the EF composite score in the RR-2 subgroup only, a relationship that was mainly due to a significant correlation between GDT net-score and WCST performance in the RR-2 group only. Thus, I only found marginal evidence for my hypothesis that deficits in the GDT are related to executive dysfunctions in MS patients. Deficits in information processing speed may seem to play a more dominant role in decision making under risk across subtypes and severity of MS.

2.1. Decision making under risk and speed of information processing

Although models of decision making usually emphasize the role of higher-order executive functions in decision making and decision making under risk in particular (see next section), there are findings that point to a role of more basic speed of information in decision making. For example, a study by Henninger et al. (2010) investigated the relationship between decision making under risk and changes in cognition in *healthy* aging. While older adults made more risky (low-

odds) choices in the CGT than younger adults, this reduction was explained by age-related decrements in processing speed (and memory). Results from one study with *MS patients* demonstrated that choice deliberation times in the CGT were negatively correlated with a test of processing speed and attention (the PASAT) (Simioni et al., 2012). Jones and others (2011) found in an fMRI study that probing a sense of urgency in a betting game by presenting a ticking clock next to the gamble, evoked recruitment of striatal and insular responses (see also (Mather & Lighthall, 2012), linked to increased selection and behavioural execution of reward-related actions and increased affective processing, respectively, in decisions (i.e., bets) made under time pressure. A large body of research has shown that time-pressure can bias deciders towards riskier choices (e.g., Ahituv, Igbaria, & Sella, 1998; Payne, Bettman, & Luce, 1996; Young, Goodie, Hall, & Wu, 2012) although such effects are qualified by the decision making situation and/or cognitive style of the decision maker (e.g., whether or not the subject is considered to default to making decisions based on objective analysis or intuition [Allinson & Kolcz, 1996; Sarmany-Schuller, 2010]). In neuropsychological contexts, the role of processing speed in decision making under risk has been less often studied than that of executive functions (see below). However, processing speed impairments are usually considered as the primary cognitive deficit in MS (e.g., DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Demaree, DeLuca, Gaudino, & Diamond, 1999; Denney, Lynch, Parmenter, & Horne, 2004; Diamond, Johnson, Kaufman, & Graves, 2008). Thus, even though the GDT unlike the CGT is *not* a timed task, one could argue that MS-typical decrements in processing speed may have contributed to my findings. In fact, as an alternative to the perspective that processing speed is a distinct and separate hallmark cognitive impairment in MS patients (Archibald et al., 2004; Deloire et al., 2005; Randolph et al., 2005; Rao, 1986), it has been argued that deficits in speed of information processing may be a domain-general deficit that underlies other cognitive impairments in MS patients, including executive dysfunctions and extending even to untimed tasks (De Sonneville et al., 2002; Denney, Hughes, Owens, & Lynch, 2012; Drew, Starkey, & Isler, 2009;

Macniven et al., 2008; Mohr & Cox, 2001). For example, Drew and others (2009) showed that basal processing speed deficits are substantially related to executive functions in MS patients in the D-KEFS battery, especially in but not limited to timed tests with high attentional demands (e.g., switch tasks). Planning aspects in some types of executive function tasks (e.g., Tower of London) have also been found influenced by MS patients' processing speed deficits (Denney et al., 2012). Of note, in some such tests, MS patients may perform as well as healthy controls if they are given enough time to plan their strategy (Denney et al., 2012; Owens, Denney, & Lynch, 2013). Even though the GDT was not administered under any time restriction, some features of the task may induce time pressure and prompt a decision. For example, the GDT presents each trial with a video of a hand shaking the cup with the die and a rattling noise that accompanies this video. While the video is played in a loop until a decision is made, the sound subsides within less than 10 seconds. Thus, the auditory feedback could be interpreted as a prompt to make a decision at the time the sound ends. Therefore, one could speculate that the MS patients, as a whole, perhaps required more time to adequately plan their next decision, and were therefore urged into premature and more risky decisions than the controls. Unfortunately, the GDT version I used did not record decision deliberation times[3], but I would expect an even more pronounced difference between patients and controls in such measure.

2.2. Decision making under risk and executive functions

The GDT usually covaries more strongly with the level of executive functions rather than information processing speed (e.g., Brand, Fujiwara, et al., 2005; Brand, Kalbe, et al., 2005; Brand, Labudda, et al., 2004). It has been proposed that disturbances in fronto-striatal signalling, especially between striatal and DLPFC regions (Brand, Labudda, et al., 2004) and extensive structural

[3] This is mainly for historical reasons. The task was first used in severely compromised patients with alcoholic Korsakoff Syndrome (Brand, Fujiwara, et al., 2005), who were not able to operate the computer keyboard reliably. Therefore, the experimenters operated the GDT instead of the patients in this study, and the design of the GDT was kept this way in the following years. Newer versions of the task (2011and following) include recordings of reaction times.

damage to the PFC (Euteneuer et al., 2009) may underlie deficits in decision making under risk. In addition, even in healthy participants, non-advantageous decisions under risk in the GDT are related to relatively low performance on tests of executive functions (Brand, Laier, et al., 2009; Schiebener, Zamarian, Delazer, & Brand, 2011). Thus, the trend correlation between EF and the GDT in the RR-2 subgroup was in accordance with these assumptions. The association between GDT and EF in the RR-2 subgroup could be largely attributed to performance in one task score, correct sorts in the WCST. My findings here are nicely mirrored by multiple other studies that have demonstrated that GDT net-score correlates with performance in the MCST (Nelson, 1976) or the WCST (Bagneux et al., 2012; Brand, Fujiwara, et al., 2005; Brand, Kalbe, et al., 2005), and implies the involvement of specific executive functions such as categorization and set-shifting in the GDT (e.g., Brand, Fujiwara, et al., 2005; Brand, Kalbe, et al., 2005; Brand, Labudda, et al., 2004). Since some of the other measures in my EF composite measure (TOH) correlated (non-significantly) with the GDT net-score in the reverse direction, the emergence of a significant relationship between the tests in the overall EF composite score and the GDT was likely stunted. Thus, measurement issues with the composite scores may have played a role in the precision in my ability to derive a reliable executive function (EF) composite (the inclusion of such artificial TOH time scores to account for patients who did not complete all 3 trials of the task). As mentioned in the Methods section (**Section III-4**), theoretical rather than statistical considerations were employed to group my test scores into composite measures due to the limited sample size. While several timed tasks were grouped into the SOIP, resulting perhaps in a more homogeneous composite score, executive function tests were likely more heterogeneous. It remains possible that a further subdivision of the EF composite into subcomponents would have been more appropriate, although such approach would have imposed reductions in power due to a higher number of corrections for multiple comparisons. In summary, despite my expectation of a correlation between the GDT and executive functions in my sample, based on the relatively higher homogeneity of tests included in the SOIP composite score as well as the

prominence of processing speed deficits in MS in general, processing speed may have been the better indicator of decision making under risk in my sample.

Of note, the marginal correlation between EFs and the GDT in the RR-2 subgroup was also reflected by a subjective measure of executive deficits. This subgroup personally endorsed higher levels of executive dysfunction ("initiate/sustain" factor in the DEX questionnaire). The relationship between the GDT and patients' self-report of their difficulties for "initiating and sustaining actions in the widest sense" (Bodenburg & Dopslaff, 2008, p. 76) in the DEX demonstrates that my MS-patients with objectively impaired executive functions (i.e., the RR-2) demonstrated insight into their executive problems. Other studies have found a relationship between decision making and DEX scores such that MS patients with DEX scores higher than the sample's median showed significantly slower learning (Kleeberg et al., 2004) and riskier decision making in the IGT (Simioni et al., 2008). More broadly, a study by Lima et al. (2007) found that MS patients with higher DEX scores were significantly more cognitively impaired. However, two other studies have found that DEX ratings did not significantly correlate with cognitive performance (Chan, R. C., 2001; Smith, M. M. & Arnett, 2010). These findings indicate that although MS patients may not be considered accurate estimators of all aspects of their cognitive, emotional and behavioural competencies (especially when validated against more objective measures), a subgroup of patients (RR-2 patients) may be experiencing executive deficits and were able to appropriately report them.

Interestingly, in all MS patients, none of my self-report psychosocial questionnaires were related to GDT performance. However, it is worth noting that my patient sample did not report any particularly increased psychosocial symptoms in the first place (other than fatigue, a neuropsychiatric symptom is commonly more severe in this patient population). Nonetheless, the lack of a correlation may indicate that the decision making deficits here were somewhat distinct from mood, fatigue, and perceived physical and cognitive handicap. This may again speak to the greater role of cognition, compared to the influence of emotional aspects, in decision making under risk.

2.3. A role of sample characteristics and disease course?

Compared to the RR-1 and the SP patient subgroups, the RR-2 subgroup was most impaired in the GDT and across all of the composite scores. What could be distinguishing characteristics of the RR-2 patients compared to the RR-1 and SP subgroups? As already argued above, some of the RR-1 patients may be considered to have had a benign subtype of MS, and the SP patients were already in a stable state of disease progression without experiencing any remissions. In this regard, a decision making under ambiguity study by Simioni et al. (2008) found a distinct difference within RRMS patients in executive functions: RRMS patients without recent (>15 months) relapses had higher executive function scores than patients with recent relapses. Although I did not measure relapses in my study, it is possible that the RR-1 subgroup (given their relatively minimal neurological disability, EDSS $\leq$ 2.5) was somewhat stable in terms of disease progression (i.e., considered to have benign MS), whereas the RR-2 subgroup could be considered less stable (i.e., perhaps experiencing more attacks or episodes) that could have contributed to greater neurological disability and may eventually result in these RR-2 patients' transitioning into a SP subtype. The conversion from a RR to a SP subtype is marked by an increase in cognitive impairment (Benedict, Carone, et al., 2004; Filippi et al., 1994), accompanied with accelerated degeneration of the cerebral GM (Fisher et al., 2008) . Perhaps the apparent increase in cognitive dysfunction as well as decision making impairment in the RR-2's may reflect a currently less stable disease state than in both RR-1 and SP patients here.

3. Decision making and MS-related brain atrophy

In accordance with my third hypothesis, GDT performance significantly correlated with linear measurements of brain atrophy in MS patients, indexed by ICD, ICR and TVW. The same measures were also associated with my processing speed.

I calculated four linear atrophy measures including FHW, ICD, ICR and TVW. Such measures have been in use for decades (e.g., Butzkueven et al., 2008;

Caon et al., 2003; Fox, N. C. & Freeborough, 1997; Frisoni et al., 1996; Gomori, Steiner, Melamed, & Cooper, 1984; Scheltens et al., 1992; Tekok-Kilic et al., 2007; Turner et al., 2001) in a variety of neurodegenerative conditions. There is growing importance of assessing neurodegeneration/brain atrophy in addition to focal lesions or total lesion load in MS (see **Section II-1.6.1**), as well as wide availability of clinical MR scans in MS patients (i.e., scans acquired without specialized MR sequences used in more targeted MR research in MS). Thus, the utility of applying simple linear measures on standard MRs to approximate measures of brain atrophy should not be underestimated (Martola et al., 2008; Nakamura & Fisher, 2009), even though more sophisticated neuroimaging approaches certainly allow further insight into brain structure-function relationships in MS. Two-dimensional measures of brain atrophy are associated with volumetric (3D) measures of whole brain atrophy (Sharma et al., 2004) and can be sensitive to disease progression as well as clinical status (Bermel et al., 2002; Caon et al., 2003; Simon et al., 1999). The TVW and ICR in particular are often associated with cognitive impairment, even when controlling for whole-brain atrophy and lesion load (Benedict, Weinstock-Guttman, et al., 2004; Bermel et al., 2002).

3.1. Neural substrates of decision making in MS

Prior to my study, Roca et al. (2008) had been the only study to investigate any neural substrates of decision making in MS patients. Roca et al. used DTI and a decision making under ambiguity task (the IGT) in a sample of 12 RRMS patients with mild disability (EDSS $\leq$1.5) and disease duration ($\leq$3 years). Roca and others tested patients' fractional anisotropy (FA) and apparent diffusion coefficients (ADC) in orbitofrontal, fronto-lateral, frontomedial and gyrus cinguli WM, compared to a sample of healthy controls. They did not find significant relationships between the integrity of patients' frontal lobe WM tracts and decision making performance in their small sample. Although one could expect correlations between IGT performance and particularly orbitofrontal WM based on prior IGT findings with VMPFC/OFC lesion patients (Bechara et al., 2000),

MS-patients' decision making impairment emerged in the final block of the task only and not the entire task. That is, those segments of the IGT thought to reflect cognitive/executive aspects of decision making were impaired in this sample, whereas task segments that rely more on feedback-related (VMPFC/OFC-dependent) processes, were not (cf. Bechara, 2004; Bechara et al., 2005). In accordance with this finding then, OFC WM diffusivity was not significantly altered in patients (and neither was diffusivity in the cingulate gyrus). Instead, fronto-lateral (and less so, fronto-medial) WM integrity, even though uncorrelated with IGT performance, showed marked decrease in patients. Fronto-lateral WM integrity was further correlated with processing speed and a number of executive functions. Thus, although Roca and others' findings remain elusive with regard to neural substrates of decision making impairment in MS, one could expect that executive rather than emotional deficits were driving patients' deficits in the IGT in their sample. Even though there were no correlations between decision making and any of the DTI measures, finding relationships between processing speed and lateral frontal WM integrity implies a possible disturbance of subcortical–lateral frontal signalling in MS that may also have contributed to the select deficits in later IGT blocks in their sample.

Labudda et al. (2008) showed that an adaptation of the GDT for the use in functional MR imaging was associated with BOLD responses in DLPFC (rather than VMPFC/OFC), along with activations of the posterior parietal and anterior cingulate cortex in healthy elderly individuals. Such activation pattern is in general accordance to findings of associations between GDT and executive functions. Of note, the fMRI adaptation in this study removed the feedback component of the GDT so that neural substrates of choice strategy based on explicitly provided probabilities alone could be investigated. In addition to the DLPFC activation that may have been particularly critical for the executive function component in their study, observing parietal activation could point to an extended network of brain regions involved in decision making with explicit rules, including the fronto-parietal attention network involved in directing attention toward relevant information during other goal-related decision making

processes (Chelazzi, Perlato, Santandrea, & Della Libera, 2013; Kastner & Ungerleider, 2000). Interestingly, a follow-up study with the same modified GDT (a version of the GDT without feedback) in cognitively-intact PD patients found reductions in BOLD responses in patients only in parietal cortical regions (Labudda et al., 2010). Pathology in subcortical (nigra-striatal) structures is a core feature of PD (Stoessl, 2012), but engagement of activity in such regions was deliberately avoided by omitting the reward-related aspects of the task, regions that would presumably involve subcortical reward-circuitry. The remaining activity differences between PD patients and controls in Labudda et al. (2010) were confined to the parietal portions of the fronto-parietal attention network, areas found to be involved in this GDT variant in controls (Labudda et al., (2008).

That is, similar to my results, the sensitivity of some aspects of the GDT to processing speed/attention, in addition to executive functions, seems mirrored by these previous findings. Of note, the fronto-parietal attention network also incorporates subcortical brain regions (i.e., the thalamus, basal ganglia) (Stoessl, 2012) that are implicated in a variety of neurodegenerative disorders including MS (Faivre et al., 2012; Mesaros et al., 2008; Morgen et al., 2007; Sperling et al., 2001). The caudate nucleus specifically might be responsible for coordinating sensorimotor information, such as initiating and selecting an appropriate response (Grahn, Parkinson, & Owen, 2008). Grahn et al. (2008) also propose that the caudate nucleus, based on an assessment of action-outcomes, may contribute to goal-directed behaviour through the instigation of action sequences to meet the larger goal of a given activity or task. The caudate also seems to be involved in the reinforcement of an action (Grahn et al., 2008). The thalamus is involved in integrating both sensory and motor inputs from numerous cortical areas and then selectively gating and disinhibiting processes in the prefrontal cortex (Narayanan, 2003). Perhaps atrophy of these subcortical regions (indexed by enlarged ICD, ICR and TVW) might have led to a disruption of the subcortico-fronto-parietal attention network involved in explicit decision making. Additionally controlling for the contribution of processing speed in the atrophy-GDT correlations rendered these correlations insignificant or trend effects. That is, much of the GDT-atrophy

correlations were driven by processing speed. However, trend effects were still present (between ICR [p<0.08]/ TVW [p<0.09] and GDT). Thus, aspects of the GDT other than processing speed/attention-related aspects (e.g., reward –related elements), still presented here and a larger sample size may well have rendered these trends significant.

Taken together, the observed correlations between GDT and processing speed deficits on the one hand, as well as shared correlations of both GDT and processing speed with ICD, ICR and TVW on the other, could indicate dysfunction in thalamo-cortical and attention network areas underlying decision making under risk in my the MS patients here. Elements specific to the GDT and not subsumed under processing speed/attention were likely present, but their precise cortical/subcortical representation remains to be tested further in MS.

3.2. Ventricular enlargement and cognition in MS

Linear measurements of ventricular enlargement can accompany disease severity/progression in MS patients (e.g., Bermel et al., 2002; Butzkueven et al., 2008; Caon et al., 2003; Martola et al., 2008; Simon et al., 1999) and can also serve as indicators of cognitive dysfunction (e.g., Beatty & Goodkin, 1990; Benedict, Weinstock-Guttman, et al., 2004; Berg, D. et al., 2000; Butzkueven et al., 2008; Martola et al., 2008; Simon et al., 1999). In my study, among four linear measures, ICD, ICR and TVW significantly correlated with the speed of information processing composite score in MS patients. Both ICD and ICR (also known as the "bicaudate ratio [BCR]") were related to information processing speed in previous studies (e.g., Benedict, Weinstock-Guttman, et al., 2004; Bermel et al., 2002). Other studies have also found TVW and cognition to be highly related in MS patients (Benedict, Bruce, et al., 2006; Benedict, Weinstock-Guttman, et al., 2004; Sanchez et al., 2008; Tiemann et al., 2009). For example, TVW has been shown to be a strong indicator of intellectual and memory dysfunction (Rao et al., 1985). We did not find correlations between memory and any of the atrophy measures; perhaps due to our linear measures not being sensitive to the neural correlates of memory.

More similar to my results, thalamic atrophy has been related to impaired processing speed/working memory in MS patients (Houtchens et al., 2007). Since the thalamus is in close proximity to the third ventricle (e.g., Benedict, Carone, et al., 2004; Houtchens et al., 2007), therefore, my finding of a correlation between TVW and reduced processing speed is reassuring. Notably, standard neuropsychological tests are more sensitive to GM than WM changes. However, information processing speed requires integration of information between GM regions along WM tracts (Penke et al., 2012). Further study of WM-specific changes in MS and their correlations with processing speed deficits is therefore worthwhile pursuing.

FHW did not significantly correlate with decision making or any of my cognitive scores. The FHW is an anatomically large, complex and irregularly shaped structure, and therefore, it may be particularly sensitive to the effects of inter-individual variability rather than the effects of disease progression alone. Previous MS studies have also found FHW insensitive to disease progression and associated dysfunctions, especially in comparison to the usefulness of TVW (Berg, D. et al., 2000; Butzkueven et al., 2008; Simon et al., 1999). Although I had hypothesized that executive functions would be related to GDT performance, I did not see robust correlations with my EF composite score and GDT in my entire sample. Thus, given the lack of a correlation between the GDT and EF across all patients, it was not surprising that FHW did not emerge as the most relevant indicator of decision making in my sample. Additionally, FHW was also not significantly related to disease-related variables.

There was a marginal correlation between EDSS and ICR. ICR has been reported to be a sensitive indicator of MS disease progression as well as severity of associated disability (EDSS) (cf. Rao et al., 1985). For example, Caon and others (2003) found strong correlations between ICR and EDSS in a larger sample (n= 190) of MS patients. Butzkueven et al. (2008) found moderate correlations between the EDSS and the ICD (as a reminder, the ICD measure is represented in the ICR measure) in their RRMS patient sample, a correlation that was maintained over the course of 4 years and as the patients' disease and disability

continued to worsen. I also found a significant correlation between TVW and disease duration. A study by Wzylezinska et al. (2003) found that thalamic volume was negatively correlated with disease duration in RRMS patients. Interestingly, ICR was marginally related to EDSS, while TVW was marginally related to age of disease onset and significantly related to disease duration. These differences might suggest that ICR and TVW are differentially sensitive to distinct and separate aspects of disease progression/status. The predominance of motor components in the EDSS may have increased correlations between linear measures that provide a better estimate of basal ganglia-associated atrophy (i.e., neurological and motor deficits), than the thalamus-associated (TVW) measure.

It should be mentioned that I controlled for sex and age and in my correlations involving the linear measures (Raz & Lindenberger, 2010; Salonen et al., 1997). Age was controlled for since volume reductions in the whole or specific parts of the brain are a part of normal aging (e.g., Ge et al., 2001), and to disentangle the confounding effects of age and disease duration. Normal age-related thalamic reductions (Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004), for example, are associated with cognitive slowing (Van Der Werf et al., 2001). Additionally, I controlled for sex to account for possible differences in skull sizes between males and females (Jensen & Johnson, 1994). [4]

Finally, I should note that ICD was marginally different and ICR was significantly different between the patient subgroups. Therefore, the ICR was useful to distinguish subgroups here. Although a few studies found a lack of sensitivity of linear atrophy measures to MS *subtype* (RRMS, SPMS and PPMS) and disease progression/disability (Fox, N. C. et al., 2000; Kalkers et al., 2002; Martola et al., 2008), Benedict et al. (2006) found that central atrophy was greater in RR patients, and significantly greater still in SP MS patients, as compared to healthy controls. In an effort to preserve statistical power in the partial

[4] Of note, the ICR takes skull size into account by adjusting the ICD by the transverse width of the brain. Partial correlations involving the ICR might therefore have been over-corrected. Recalculating all partial correlations between ICR, disease parameters, and cognition (including GDT) as simple Pearson correlations (not correcting for age or sex) gave very similar or stronger results. For consistency with the other atrophy measures, partial correlations are reported here.

correlations between atrophy measures and disease parameters/cognition had to include the entire patient sample here. Future studies with larger sample sizes in patient subgroups should be conducted to delineate whether there might be a differential sensitivity for certain atrophy measures to covary with disease parameters/ cognition in specific MS subtypes.

4. Study limitations

There are a few limitations to my study. One limitation was my small sample size, especially for my patient subgroup analyses (i.e., when I compared the controls with RR-1, RR-2 and SP separately). These analyses were conceived of after I had started collecting data, and therefore in future studies should be accommodated in advance to ensure equal distribution of participants across groups and larger subgroups overall. I should mention here though that apart from Simioni et al.'s studies (2008: n=165; follow-up study of a sub-sample of the same patients in 2009: n= 70; 2012: 2012: n=72, with an undeclared relationship to their prior samples), my overall sample size with 32 patients was larger than samples in other decision making studies in MS.

As previously mentioned, the generation of composite scores of neuropsychological performance was driven by theoretical considerations, since my healthy control sample was not sufficiently large to accommodate more sophisticated statistical approaches (such as principal component or factor analyses). Such derivation of composite scores does involve some subjective assignment by the researchers and can be biased. For example, there can be shared functional involvement of tests across composite scores although each test is only counted towards one composite score. A lack of involvement of theoretically meaningful tests within certain composite scores can also occur (e.g., as was found for the TOH time-to-completion variable within the EF composite score), as well as an overrepresentation of certain tests within composite scores (e.g., the SRT being the only memory measure). Again, a larger sample, including a higher number of healthy controls could overcome some such limitations, in

addition to a more comprehensive cognitive battery spanning additional cognitive domains (e.g., visual memory).

It should also be mentioned explicitly here that the GDT is a laboratory test of decision making abilities; the test is not necessarily reflective of the "riskiness" of a participant's decisions on a daily basis, and cannot be generalized to assume an individual will always perform in this manner when making all decisions. Factors like experience, emotional state, external factors, incentives, available feedback, etc., in addition to one's cognitive abilities, will influence decision making in the real world (and many of these variables are controlled or reduced in a test setting such as here).

With regard to an unexplored factor that may have influenced cognitive performance in my study, patients' medications should be considered. The majority of CNS-active drugs are known to have an effect on cognition, but it is difficult to determine *additional* cognitive dysfunctions caused by medications in individuals who already experience some cognitive impairment (i.e., MS patients) (see Oken et al., 2006) for a study of the effects of CNS-active medications on cognition in MS patients). As described in the Participants **Section III-1** (see also **Table III-5**), I had originally intended to exclude psychotropic drugs (e.g., benzodiazepines and anticonvulsants). During recruitment, I had to broaden this exclusion criterion, due to the clinical reality that very few patients in more advanced disease stages (i.e., SPMS patients) are free of any such medications. Since type/dosage of medications and MS severity/subtype are usually confounded, I abstained from further analysis of cognitive performance as a function of medication here. Even if I had attempted such breakdown, the extent that a given medication had potentially influenced cognitive performance would still be obscure, since I would have had no baseline measure (without medication). Instead I provided a detailed, qualitative overview on patients' current medications (see **Table III-5**).

A few limitations with regard to the structural MR measures should be mentioned. First, images were obtained for MS patients and control patients, but

not for healthy controls. Although I was able to compare the linear measurements between two groups in order to establish evidence of the effect of MS-related pathology on ventricular enlargement, I could not analyze the relationship between cognition and brain atrophy in any sample other than my MS patients. Also, a closer matching between scan acquisition and test date for my MS patients would be desirable (our acquisition time ranged from 3 weeks to 31 months; mean=42.51 weeks). Moreover, given that I used clinical MR scans, the scan protocols as well as scanner hardware differed across patients, and this could introduce noise into my linear measures (although most were standard clinical scans with 5 mm slice thickness acquired with a 1.5 Tesla magnetic field strength). Scheduling a more standardized MR session closer to the test session would increase my methodological precision in this regard. Finally, the use of a manual procedure to obtain the linear measurements can reduce the reproducibility of the measures, even if, as here, intra-rater reliability may be high and average scores across multiple measurement time points are used. Additional application of automated (rather than manual) segmentation procedures are of particular value to avoid issues with reliability, although these methods are associated with other problems (e.g., tissue misclassification issues in the presence of MS-specific lesions) (cf. Bermel & Bakshi, 2006).

5. Future directions

There are a few future directions that I can suggest based on my results and previous results from other studies. I observed most pronounced deficits in the RR-2 group and suggested that this might have been related to the fact of impending conversion to the SP disease course. Thus, a longitudinal follow-up of my MS patients' decision making abilities would be worthwhile. Since only one longitudinal study about MS patients' decision making abilities has been conducted, using the IGT (Simioni et al., 2009), a longitudinal MS-study on decision making under risk, ideally including measures of neurodegenerative changes, would be a valuable addition to the existing literature. A more sophisticated assessment of MS-related brain changes as they relate to decision

making deficits would also be most valuable, considering the relatively coarse measure of atrophy I used here.

No decision making study thus far has currently recruited PPMS patients, likely because only about 10-15% of all MS patients are of the PP subtype. Including PPMS patients, to a RR and SP patient sample, would allow me to test differences in decision making across the three subtypes, types that differ with regard to epidemiology, disease outcome/prognosis, MRI and neuropathological findings, as well as clinical outcomes (Lucchinetti et al., 2000; Thompson et al., 1991; Thompson et al., 1997). The precise differences in cognitive impairment between PPMS and SPMS patients are debated. Both may be equally cognitively impaired and more substantially so than RRMS patients (Potagas et al., 2008; Ukkonen, Vahvelainen, Hamalainen, Dastidar, & Elovaara, 2009). However, as the process of conversion from RR to SPMS involves both negative effects of repeat relapses in addition to steady disease progression/ neurodegeneration (Bramow et al., 2010), SPMS patients may show even more pronounced cognitive impairment than PPMS. A possible differentiating finding *within* cognitive deficits across the two progressive MS subtypes refers to the preferential involvement of the spinal cord and subcortical brain areas in PPMS, and this may account for an even greater impairment in motor and information processing speed in PPMS than in SPMS (Huijbregts et al., 2004) (but see Denney, Sworowski, & Lynch, 2005). As the GDT was related to speed of information processing in my sample, patients with PPMS patients might be particularly vulnerable also to GDT deficits, but this remains to be tested.

Additionally, future studies could assess and compare both decision making under risk and decision making under ambiguity in MS patients by including the GDT and the IGT. Administering the IGT and GDT together could disentangle the extent that emotional and/or cognitive aspects of decision making are implicated in MS and how these relate to one another. An interesting addition would also be a GDT version without the feedback component. Both IGT and GDT contain emotional and cognitive elements of decision making. The GDT allows cognitive development of decision strategies based on explicit rules, but

this process is supplemented by the display of rewarding or punishing feedback. In comparison, the IGT does not provide rules but only feedback instead. However, once decision rules are acquired, IGT performance relies on cognitive/executive functions. Thus, eliminating the feedback component from the GDT, as was done in other non-MS studies (Brand, 2008; Brand, Laier, et al., 2009; Brand, Pawlikowski, et al., 2009), isolates processes of decision making that are based on executive/cognitive functions alone. Including such a version of the GDT, ideally along with the IGT and the conventional GDT, would increase the level of precision in assessing mechanisms of decision making deficits across different subtypes of MS, (un-) related to disability, cognitive impairment, neuropsychiatric changes, as well as brain changes. To give a simplistic example, if cognitive dysfunctions dominate risky decision making, one would expect that MS patients are most impaired in both versions of the GDT, especially the GDT without feedback, but less so in the IGT. However, if emotional dysfunctions dominate decision making, strongest impairment should emerge in the IGT, followed by standard GDT, and least impairment in the GDT without feedback.

6. Conclusions

MS has a heterogeneous pathology, with approximately 50% patients experiencing cognitive deficits (Arnett & Strober, 2011). Cognitive deficits have been reported across all disease stages and subtypes. Decision making, an important part of daily living that may affect the quality of life of MS patients, has never been studied in this population using the GDT, a task that measures decision making under risk. This type of decision making has been more definitively related to cognitive/executive dysfunctions in other patient samples, compared to the more commonly studied decision making under ambiguity, assessed with the IGT. I found GDT decision making impairments in a sample of MS patients, composed of both the RR and SP subtype, with a wide range of neurological disability and long disease duration. Decision making performance was related to neurological disability and disease severity (i.e., EDSS). Specifically, compared to controls, GDT impairment was confined to the two

more disabled MS patient subgroups RR-2 and SP, while the relatively more cognitively and neurologically-preserved patients from the RR-1 subgroup were unimpaired. Unlike other studies that have found the GDT to be related to other cognitive/executive measures, only the RR-2 patients showed a trend correlation between decision making and executive functions, while decision making in the entire patient group correlated with processing speed. MS patients' and control patients' brain atrophy was studied with linear measurements of ventricular enlargement on clinical MRI images. Central atrophy measures (ICD/ICR) differentiated the groups, and ICD, ICR and TVW showed significant correlations with processing speed in MS patients. The same measures were also correlated with GDT performance. Given that the GDT requires a subject to integrate, plan and execute a series of decisions based on explicit rules and probabilities for how to achieve a desired outcome, the decision making process may depend on both subcortical and cortical structures as well as the WM pathways of cortico-subcortico-frontal and parietal networks. Therefore, in my MS patient sample, advantageous decision making may be related to multiple brain areas, with a particular emphasis on subcortical structures neighbouring the basal ganglia (i.e., caudate regions) and the third ventricle (i.e., thalamic regions). Since MS patients' speed of processing deficits and neurodegeneration were both related to impaired decision making, the GDT may be considered an indicator of two hallmark consequences of MS pathology.

By examining the qualitative differences in decision making impairments associated with different MS patient subtypes and levels of disability, I have gained valuable information regarding the underlying neural basis of decision making and the involvement of cognitive aspects. These results could guide the development of specific treatment options, such as training of functions like behaviour planning, monitoring, and use of performance feedback to incite greater independence, autonomy, safety and quality of life for MS patients.

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APPENDIX

Appendix A. *The Revised (2010) McDonald Criteria for the diagnosis of MS* (Polman et al., 2011).

Clinical Presentation	Additional Data Needed
* 2 or more attacks (relapses) * 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
* 2 or more attacks * 1 objective clinical lesion	Dissemination in space, demonstrated by: * MRI * or a positive CSF and 2 or more MRI lesions consistent with MS * or further clinical attack involving different site. **New criteria:** Dissemination in Space (DIS) can be demonstrated by the presence of 1 or more T2 lesions in at least 2 of 4 of the following areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord.
* 1 attack * 2 or more objective clinical lesions	Dissemination in time (DIT), demonstrated by: * MRI * or second clinical attack **New criteria:** No longer a need to have separate MRIs run; Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack. [This allows for quicker diagnosis without sacrificing specificity, while improving sensitivity.]
* 1 attack * 1 objective clinical lesion (clinically isolated syndrome)	**New criteria:** Dissemination in space and time, demonstrated by: For DIS: 1 or more T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or await a second clinical attack implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack.
Insidious neurological progression suggestive of MS (primary progressive MS)	**New criteria:** One year of disease progression (retrospectively or prospectively determined) and two or three of the following: 1. Evidence for DIS in the brain based on 1 or more T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on 2 or more T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Appendix B. *Z-scores and standard deviations of study controls' performance on the neuropsychological tests, derived from published norms.*

Neuropsychological Test Scores	Mean Z-scores	Standard Deviations
SDMT	.22	1.40
SRT Total Correct	.08	.86
SRT CLTR	-.08	.91
SRT Intrusions	.03	1.54
SRT Delayed	.34	.95
PASAT Total Correct	-.06	1.16
Pegboard right hand insertion time[1]	-.70	.98
Pegboard left hand insertion time[1]	-.74	1.38
TOH Total Trials[2]	.40	.66
WCST Total Correct	.12	.57
WCST Perseverative Errors	-.13	.74
Forward Digit Span	.42	.76
Backward Digit Span	.47	.74
COWAT Total Correct	.42	1.05

SDMT: Symbol-Digit Modalities Test, SRT: Selective Reminding Test, CLTR: Continuous long-term retrieval, PASAT: Paced Auditory Serial Addition Test 3'' version, Pegboard: Nine-Hole Pegboard Test, TOH: Tower of Hanoi, WCST: Wisconsin Card Sorting Test (64-card version), COWAT: verbal fluency test. 1: The normed Pegboard scores are separated by right and left hand which is different than my combined Pegboard score that was used for the analyses in this study (see p. 62 for a detailed explanation); [2]: The normed TOH Total Trials is a different score than the score of TOH Time that we generated and used for the analyses in this study (see pp. 71/72 and footnote 2 on p. 97 for a detailed explanation).

Appendix C. *Proportion of MS patients in each subgroup performing less than or equal to two standard deviations below controls' performance in composite scores.* Scores are frequency counts (percentages).

	RR-1 (n=13)	**RR-2 (n=9)**	**SP (n=10)**
SOIP	0 (0.00%)	0 (0.00%)	2 (20.00%)
MEM	4 (30.77%)	5 (55.56%)	3 (30.00%)
EF	1 (7.69%)	1 (11.11%)	0 (0.00%)
Global	1 (7.69%)	1 (11.11%)	0 (0.00%)

SOIP: speed of information processing, MEM: memory, EF: executive functions, Global: global cognitive functioning.