Universidade do Minho
Escola de Psicologia

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Visual processing speed deficits in Multiple Sclerosis

Janeiro de 2013

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Programa Doutoral em Psicologia
Especialidade de Psicologia Clínica

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e do
Professor Doutor Jorge Manuel Castelo Branco de Albuquerque Almeida

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Visual processing speed deficits in Multiple Sclerosis

ABSTRACT

Multiple Sclerosis (MS) is an inflammatory demyelinating disease, which usually affects adults between the ages of 20 and 50. Both at its initial stages and during the course of the disease, acute episodes of neuro-ophthalmic syndromes are frequent, and have been associated with long-term abnormalities in the visual system, even when full clinical recovery is reached. Moreover, recent studies have also reported visual system abnormalities in MS individuals without a previous history of acute episodes of neuro-ophthalmic syndromes, thus suggesting that the visual system might be vulnerable to MS. Cognitive deficits are equally frequent in MS and appear both at the initial and later stages of the disease's progression. Processing speed is probably one of the most common cognitive deficits in MS.

Despite the fact that both visual abnormalities and cognitive impairment are common in MS, the complex interaction between these two is not completely understood. The current study aims to contribute to a further understanding of the interaction between these types of impairments by assessing visual processing speed deficits in relapse-remitting MS (RRMS). Specifically, it is our objective to understand whether the history of neuro-ophthalmic syndromes might be related with worse performances in vision-based processing speed tasks in RRMS participants with normal or corrected-to-normal visual acuity. Additionally, we propose to study how putative abnormal temporal properties of visual processing might be related with processing speed deficits, which was assessed through neuropsychological and psychophysical tasks.

In the first study, results suggest that having a history of the neuro-ophthalmic syndromes is related with poor performance in vision-based processing speed tasks. MS individuals with a history of neuro-ophthalmic syndromes still present, however preserved capability to perform visual tasks. Since long-term abnormalities often occur after this clinical event, we hypothesized that visual system defects might contribute to visual processing speed deficits, commonly found in MS.

In the second study, it was demonstrated that processing speed deficits were associated with a decreased capability to detect fast presentations of visual stimuli, as well as with a higher limitation in temporal processing capacity. Moreover, the temporal dynamics of visual processing seem to be compromised, on average, for participants with multiple sclerosis, regardless of their cognitive performance. For instance, for multiple sclerosis participants with processing speed deficits, the problem seems not to be an impaired capacity to perform a recognition task or process visual information, but rather lower temporal processing capacity of the visual system.

These results might be an expression of a latent sensorial temporal limitation of the visual system in participants suffering from relapse-remitting multiple sclerosis, perhaps contributing significantly to the processing speed deficits found. The potential neural causes for the presented results will be discussed. Furthermore, implications for rehabilitation and future studies will also be presented.

Défices de velocidade de processamento visual na Esclerose Múltipla

RESUMO

A Esclerose Múltipla (EM) é uma doença inflamatória desmielinizante, que afeta adultos entre os 20 e os 50 anos de idade. Tanto em fases iniciais como no seu decurso, é frequente a existência de episódios de síndromes neuro-oftálmicos que resultam em alterações do sistema visual a longo-prazo, mesmo em casos onde se regista uma recuperação clínica total. Estudos recentes indicam que alterações ao nível do sistema visual podem igualmente aparecer em pessoas sem historial clínico de alterações visuais, sugerindo desta forma que na EM o sistema visual poderá ser vulnerável. Défices de funcionamento cognitivo são também frequentes, sendo o défice de velocidade de processamento provavelmente um dos mais comuns.

Apesar das alterações visuais e dos défices cognitivos serem frequentes na EM, a interação entre ambos é pouco conhecida. A presente dissertação visa contribuir para o aumento do conhecimento sobre os défices de velocidade de processamento visual em indivíduos com EM do tipo remissivo-recorrente. Para o efeito, pretende-se compreender de que forma a história de episódios agudos de síndrome neuro-oftálmico poderá estar relacionada com piores performances em testes neuropsicológicos de avaliação da velocidade de processamento, em participantes com EM do tipo remissivo-recorrente, com acuidade visual normal (primeiro estudo). No segundo estudo, analisa-se a associação entre défices de velocidade de processamento, avaliados através de testes neuropsicológicos, e potenciais alterações ao nível das propriedades do processamento temporal (segundo estudo).

No primeiro estudo, os resultados evidenciam a existência de uma associação entre a presença de um historial de síndrome neuro-oftálmico e piores desempenhos em testes de velocidade de processamentos visual, apesar da capacidade de realização de tarefas visuais estar preservada. Tal situação sugere que as alterações ao nível do sistema visual, frequentemente associadas a episódios de síndromes neuro-oftálmicos, poderão contribuir, de forma significativa, para os défices de velocidade de processamento avaliados com testes neuropsicológicos visuais, comummente associados à EM.

No segundo estudo, os resultados indicam que os défices de velocidade de processamento estão associados a uma diminuição da capacidade de deteção de estímulos visuais rápidos, assim como, a uma maior limitação ao nível da capacidade de processamento temporal. Constata-se ainda que as dinâmicas temporais do processamento visual parecem estar comprometidas na EM, independentemente da performance cognitiva. Segundo estes resultados, os défices de velocidade de processamento na EM estão relacionados com uma limitação na capacidade de processamento temporal do sistema visual, apesar de estar preservada a habilidade de reconhecer e processar adequadamente informação visual.

Os resultados comportamentais descritos parecem dever-se a uma limitação sensorial latente do sistema visual em participantes que sofrem de EM do tipo remissivo-remitente, contribuindo significativamente para os défices de velocidade de processamento encontrados. Uma discussão acerca das potenciais causas neurais para os resultados comportamentais apresentados, e implicações para o desenvolvimento de futuras investigações e intervenções de reabilitação neste âmbito, serão ainda apresentadas.

ABBREVIATIONS

AON – Acute Optic Neuritis

BDI – Beck depression inventory

CNS – Central Nervous System

CSLO – Confocal scanning laser ophthalmoscope

EDSS – Expand Disability Status Scale

ERP – Event-related potentials

FFA - Fusiform face area

fMRI – Functional Magnetic Resonance Imaging

LOC – Lateral occipital cortex

MCM – Metacontrast Masking

MRI – Magnetic Resonance Imaging

MS – Multiple Sclerosis

OCT – Ocular Coherence Tomography

ON – Optic nerve

PE – Prior-entry

PPA - Parahippocampal place area

PPMS – Primary progressive multiple sclerosis

RNFL – Retina Nerve Fiber Layer

RRMS – Relapse-Remitting Multiple Sclerosis

RSVP – Rapid Serial Visual Processing

SLP – Scanning laser polarimetry

SPMS – Secondary progressive

VEP – Visual evoked potential

INDEX

FIGURE INDEX

TABLE INDEX

ANNEX INDEX

INTRODUCTION TO MULTIPLE SCLEROSIS

The introductory chapters aim to give a brief description of Multiple Sclerosis (MS), specially focusing on the neuro-ophthalmic and cognitive aspects of the disease.

Introduction

MS is an inflammatory demyelinating disease, which usually affects adults between the ages of 20 and 50 (Kantarci & Wingerchuk, 2006). The National Multiple Sclerosis Society has estimated that approximately 400,000 individuals are affected by MS in the United States (www.nationalmssociety.org). Despite the fair amount of research, the cause or causes of MS, still remain under study. The hypothesis, which gathers greater consensus, proposes that MS is an autoimmune disease, probably induced by a viral or other infectious agent. Although it is known that genetic and environmental factors are involved, their interaction remains uncertain (DeLuca & Nocentini, 2011).

Diagnosis

Diagnosis is established by clinical assessment and magnetic resonance imaging (MRI), and is based on a consensus between the two regarding the existence of white-matter disease. To establish a diagnosis of MS, and in accordance with McDonald's criteria, the disease must be disseminated in space and time (McDonald et al., 2001; Polman et al., 2011). Dissemination in space requires ≤1 T2 bright lesions in two or more of the following locations: periventricular, juxtacortical and infratentorial. Dissemination in time can be established as a new lesion when compared to a previous scan or the presence of an asymptomatic enhancing lesion and a non-enhancing T2 lesion on any scan.

Complementary exams, such as electrophysiology and cerebrospinal fluid examination, might be of particular help (Miller, McDonald, & Smith, 2007).

Epidemiology

Geographic factors influence the prevalence of MS (Compston & Confavreux, 2007; Kurtzke, 2000). Countries located in North America or in northern Europe present a high prevalence of MS (estimation of <100 cases per 100 000), followed by the southern regions of the USA and Europe (with an average prevalence 10-80 cases per 100 000). Countries located in Asia, South America and Africa present low prevalence of the disease (1-15 cases per 100 000). Although an increased prevalence as one moves away from the Equator has been well documented, recent studies have reported a weaker effect than was previously observed (Zivadinov et al., 2003). MS is twice as common in women as in men.

The course of MS

The course of the disease is not homogenous across individuals or even within the same individual over the years. Four disease courses are the most prevalent and their severity varies from mild, moderate to severe.

The disease may be characterized by acute exacerbations of symptoms (relapses), followed by a partial to total recovery of function, without progression of disability between syndromes. In this case, it is denominated as relapse-remitting MS (RRMS).

About 85% of individuals with MS, present a RRMS course at onset. During the first 10 years after diagnosis, approximately 50% will probably develop a secondary progressive form (Lublin & Reingold, 1996).

The secondary progressive (SPMS) course is characterized by an initial period of RRMS, which frequently leads to a progressive worsening of neurological functioning, where only minor improvements are registered. The transition from RRMS to SPMS, although frequent, varies significantly in the time course of transition across individuals.

Approximately 10% of MS individuals present a primary-progressive (PPMS) course, characterized by continuous progression from the onset of the disease, stationary phases or mild and transient improvement might sometimes occur.

The progressive-relapsing (PRMS) course is rather rare (about 5%) and is characterized by constant worsening from the onset of the disease, with marked attacks over time, where long-term recovery will vary, if at all.

While RRMS is the most prevalent course for early onset cases (when initial symptoms occur at an early age), for late onset cases (occurring at an older age, i.e. above 50) a primary progressive course is more frequent.

Recently, there has been growing interest in another potential course of the disease - the so-called 'benign form of MS' (Amato et al., 2006a; Benedict & Fazekas, 2009). In the past, the benign course was established on the basis of the level of disability, which is usually low (an Expanded Disability Status Scale – EDSS - ≤3) and which remains for at least 15 years after diagnosis. An increase in the number of years after diagnosis of 20-25 years, and the consideration of all neurological functions, even cognition, were recently proposed modifications for the establishment of the benign course.

Clinical profile and symptoms

The clinical profile of MS is extremely heterogeneous, affecting motor and cognitive functions, as well as leading to neuropsychiatric issues, among others (Brassington & Marsh, 1998). Symptoms are caused by unpredictable and progressive episodes of axonal demyelination that compromise the conduction of electrical potentials along the neural pathways in the central nervous system. These episodes can result in lesions along the axons of nerve fibers in the brain, brain stem, spinal cord, and optic nerve (Prakash, Snook, Lewis, Motl, & Kramer, 2008).

Symptoms such as motor disability, visual deterioration (Frohman, Graves, Balcer, Galetta, & Frohman, 2010; Maxner, 2006), cognitive function impairment (Caramia, Tinelli, Francia, & Pozzilli, 2010; Chiaravalloti & DeLuca, 2008), fatigue (DeLuca, Genova, Hillary, & Wylie, 2008) and depression (Arnett & Randolph, 2006; Wallin, Wilken, Turner, Williams, & Kane, 2006) are frequent and significantly compromise quality of life and employment.

Introduction to the studies

Visual abnormalities have been a common concomitant of MS (Balcer et al., 2003) and have been associated mainly with a history of acute episodes of neuro-ophthalmic syndromes (Frohman, Frohman, Zee, McColl, & Galetta, 2005). Likewise, over the past years of research, neuropsychological studies have consistently reported cognitive impairments in MS persons. In particular, processing speed deficits are amongst the the most frequent cognitive impairments reported (Chiaravalloti & DeLuca, 2008; DeLuca & Nocentini, 2011; Patti, 2009; Prakash et al., 2008; Rao, Leo, Bernardin, & Unverzagt, 1991). Little is known, however, about the possible relationship between visual system integrity and performance on neuropsychological tasks.

In the next two chapters, I will present a brief overview of what is known about common neuro-ophthalmic syndromes and abnormalities (chapter II), and the neuropsychological function found in MS (chapter III) found in MS.

NEURO-OPHTHALMOLOGY IN MULTIPLE SCLEROSIS

During the course of MS, acute episodes of neuro-ophthalmic syndromes are frequent and significantly affect normal visual functioning. Although clinical recovery is often reached, long-term visual system abnormalities have been found. The next chapter aims to briefly describe the most common neuro-ophthalmic syndromes affecting MS persons and their frequent long-term implications.

Neuro-ophthalmology of Multiple Sclerosis

Neuro-ophthalmic syndromes are frequent during the course of MS (e.g. Frohman et al., 2010), and are believed to be caused by episodes of inflammation, demyelination and neurodegeneration (Burton, Greenberg, & Frohman, 2011; Frohman et al., 2005). There are several and distinct neuro-ophthalmic syndromes that constrain both the visual sensory system (McDonald & Barnes, 1992) as well as the ocular motor system (Barnes & McDonald, 1992). These pathological processes recurrently lead to significant visual disturbances such as double or blurred vision, among others (a detailed description of the most frequently neuro-ophthalmic syndromes and associated symptoms can be found in Table 1).

The magnitude and duration of these visual symptoms, commonly characterized by an abrupt onset, can vary among subjects and during different episodes, and can arise unilaterally or bilaterally. Total or at least partial recovery of visual function is usually reached within weeks after an acute episode (Frohman et al., 2005; Frohman et al., 2010; Maxner, 2006).

While abnormal eye movements are believed to be associated with cerebral, midbrain, cerebellar vestibular and high cervical demyelination, as well as inflammation processes (Niestroy, Rucker, & Leigh, 2007; Prasad & Galetta, 2010), symptoms such as impaired acuity

or visual loss, color and contrast vision impairments are probably caused by pathological processes affecting the afferent visual system, such as optic neuritis (Frohman et al., 2008a; Kolappan et al., 2009; Maxner, 2006).

Acute optic neuritis (AON) is one of the most common deficiencies of the optic nerve in individuals with MS, appearing either during the first episode of MS, in about 40% to 50% of cases, or during the course of the disease, in about 80% of the cases (e.g. McDonald & Compston, 2007). AON is a deficiency of the afferent visual pathways provoked by inflammation, demyelination and neurodegeneration processes (Burton et al., 2011).

Abnormalities of the visual system often associated with MS

Although complete clinical recovery is frequently reached, studies suggest that long-term disruptions of certain components of the visual system after acute episodes of neuro-ophthalmic syndromes often occur. For instance, Talman and colleagues (Talman et al., 2010) has observed a decrease in the retinal nerve fiber layer (RNFL) thickness in MS individuals. Higher levels of atrophy of the optic nerve (Trip et al., 2006), and lateral geniculate nucleus and visual cortex atrophy are also systematically found (2007).

Anatomical and functional visual system deficits can easily be assessed by using different technologies such as ocular coherence tomography (OCT), magnetic resonance imaging (MRI) or visually evoked potentials (VEP). Below, I will present an overview of the principal results regarding the abnormalities of the visual system associated with MS.

Retinal Nerve Fiber Layer and macular thinning

Since the retina is devoid of myelin, direct quantitative measures of axonal loss can be obtained without the frequent confound originating from the demyelization processes. Some authors have therefore claimed that the retina is a good model to study MS, as well as to study the viability of neuroprotective treatment strategies (Burton et al., 2011; Frohman et al., 2006; Frohman et al., 2008b; Trip et al., 2005).

RNFL thickness and macular volume are considered to provide important information regarding the integrity of the retina, and have been traditionally accessed through optical coherence tomography (Frohman et al., 2008a). Moreover, scanning laser polarimetry (SLP) and confocal scanning laser ophthalmoscopy (CSLO) have also been used to assess RNFL thickness (Kolappan et al., 2009). All these methods have shown that the RNFL is normally thinner in MS individuals, when compared to matched healthy controls (Albrecht, Frohlich, Hartung, Kieseier, & Methner, 2007; Fisher et al., 2006; Walter et al., 2012). This thinning is presumably related with a history of acute optic neuritis (Petzold et al., 2010), MS type (Costello, Hodge, Pan, Freedman, & DeMeulemeester, 2009), as well as the degree of disability (Fisher et al., 2006).

A history of AON is associated with significant decreases in RNFL thickness in the affected eye when compared to the non-affected eye (Fisher et al., 2006; Siger et al., 2008), to the eyes of healthy controls (Almarcegui et al., 2010; Trip et al., 2005; Trip et al., 2006), and to MS

Table 1 - The neuro-ophthalmology of multiple sclerosis

Ocular motor pathophysiology			
Neuro-ophthalmic Syndrome	**Characteristics**	**Symptoms**	**Authors**
Internuclear ophaltmoplegia	Involvement of the medial longitudinal fasciculus (MLF), a heavily myelinated pathway	Adduction slowing and limitation; Abduction nystagmus (discrepant movements of the two eyes during saccades are possible, resulting in visual confusion, transient oscillopsia, diplopia, reading fatigue, and a loss of stereopsis); Low pursuit gain; Skew deviation; Vertical saccades preserved; Vergence preserved	Maxner (2006) Frohman and colleagues (2005) Niestroy and colleagues (2007) Prasad and Galetta (2010)
Nystagmus	Cerebellum; Brainstem; Vestibular apparatus either central or peripheral	Gaze-evoked nystagmus (slow drift in one direction and a resetting saccade in the other); Pendular nystagmus (back and forth slow-phase oscillation);	Maxner (2006) Frohman and colleagues (2005) Niestroy and colleagues (2007) Prasad and Galetta (2010)

Continuation of table 1			
Saccadic eye movements abnormalities	Supranuclear dysfunction Cerebellum Brainstem	Saccadic dysmetria (target fixating inaccuracies with rapid eye movement, often associated with an overshoot, followed by oscillation of saccades around the target until fixation is reached); Slow saccades (diminished amplitude movement and delayed saccadic initiation); Saccadic intrusions (ocular fixation disruption, leading to vision jumping or oscillation).	Maxner (2006) Frohman and colleagues (2005) Prasad and Galetta (2010) McDonald and Compston (2007)
desynchronization between eye and body movements	Vestibular-ocular system	Blurred vision Vision oscillation with head or body movements Involuntary loss of fixation	Maxner (2006)
Afferent visual system disorders			
	Characteristics	**Symptoms**	**Authors**
Optic Neuritis	Optic nerve inflammation and demyelination. Onset of	Pain can precede or accompany the onset of visual symptoms, occurring particularly with eye	McDonald and Barnes (1992)

Continuation of table 1			
	impaired vision is normally characterized as sudden, although patients are able to identify partial defects that worsen over hours or days, when questioned.	movements; Blurred vision; Visual acuity varies from normal to complete blindness; Optic disc abnormalities; Color and contrast sensitivity impairment; Moore's lightning streaks (induced by eye movements or certain sounds)	Burton and colleagues (2011) Shams and Plant (2009)
Other neuro-ophthalmological problems of the afferent visual system	Chiasm, tracts, radiations and striate cortex, ocular inflammation (anterior and posterior uveitis, pars planitis, and periphlebitis)	Symptomatic homonymous field defects are uncommon	Frohman and colleagues (2005) Maxner (2006)

individuals without a history of AON in either eye (Fisher et al., 2006; Siger et al., 2008; Walter et al., 2012). However, RNFL abnormal thickness in MS is highly associated with the history of acute optic neuritis, it can also be observed in eyes that have no history of AON (Fjeldstad, Bemben, & Pardo, 2011; Petzold et al., 2010; Urano et al., 2011).

The greatest decreases in RNFL thickness occur in the secondary progressive MS group, followed by the relapse-remitting groups and finally by the clinical isolate syndrome group (Costello et al., 2009; Pulicken et al., 2007).

While some studies have found significant relations between measures of disability (e.g. Expend Disability Status Scale and Multiple Sclerosis Functional Composite - EDSS) and retina OCT measures (Grazioli et al., 2008; Siepman, Bettink-Remeijer, & Hintzen, 2010), other studies have failed to find these same results (Oreja-Guevara, Noval, Manzano, & Diez-Tejedor, 2010).

To sum up, eyes with a history of AON present the greatest reduction in RNFL thickness. Nevertheless, MS individuals without a history of AON can also present abnormal values of RNFL thickness, when compared to match healthy controls. Additionally, while the degree of RNFL thickness seems to be associated with the MS type, the relation with measures of disability is controversial.

Optic Nerve

According to Parinaud (1884) and Uhthoff (1889), the optic nerve is particularly vulnerable to MS-related deficiencies. Abnormalities within the optic nerve are frequent in MS and their

severity is related, much in the same way as for RNFL thickness, with a history of acute optic neuritis (McDonald & Barnes, 1992; Shams & Plant, 2009).

Postmortem analyses reveal that 94% to 99% of individuals with MS suffered optic nerve lesions, frequently involving the retrochiasmal pathways, including the optic radiations (Kolappan et al., 2009). Optic nerve lesions may lead to the appearance of observable clinically significant symptoms (e.g., episodes of acute optic neuritis), or may be asymptomatic, where symptoms are either not substantial or imperceptible to the patient (Frohman et al., 2005; Frohman et al., 2010).

Even though visual recovery after AON is normally reached, event-related potentials and magnetic resonance imaging studies suggest that abnormalities do, in fact, remain (Burton et al., 2011; Kolappan et al., 2009). Episodes of AON have been associated with long-term abnormal cortically-generated potentials in MS. For instance, the P100, an ERP component normally associated with the early processing of visual stimulus, seems to be affected by AON. In particular, the latency of this component seems to be delayed while its amplitude tends to be preserved, when compared to healthy controls, and even after full clinical recovery (Gareau et al., 1999). However, controversial results concerning P100 amplitudes do exist Almarcegui and colleagues (2010) reported that P100 amplitude was significantly decreased for MS participants, when in contrast with healthy controls. Furthermore, during the earliest stages of AON, P100 amplitudes are frequently reduced, temporally dispersed, or are associated with a complete conduction block (i.e., severe attenuation or total absence of amplitude). The P100 delay latency is likely to be an expression of a delay in processing – i.e., participants with an AON history probably need more time to process a visual stimulus in comparison with healthy controls. Interestingly, delayed latencies are commonly associated with demyelination following

optic neuritis, whereas amplitude abnormalities are associated with inflammation and axonal loss (Burton et al., 2011).

Optic nerve atrophy in MS has been demonstrated through post-mortem analyses (Evangelou et al., 2001) and MRI studies (Kolbe et al., 2009; Trip et al., 2006). Several authors have claimed that optic nerve atrophy after AON occurs predominantly as a result of axonal loss, and also, to a lesser degree, due to the loss of myelin (Burton et al., 2011; Trip et al., 2006).

To sum up, a fair amount of research has suggested that the optic nerve is highly vulnerable to MS-related processes such as inflammation, demyelination and neurodegeneration. The severity of these abnormalities seems to be related with a history of acute optic neuritis (Kolbe et al., 2009), much in the same way as for RNFL thickness.

Lateral geniculate nucleus and visual cortex

The Lateral geniculate nucleus (LGN), as well as the visual cortex, are believed to be commonly affected in individuals with MS, with the severity of these deficiencies, once again, being related to the history of AON episodes (Evangelou et al., 2001; Gareau et al., 1999). However, there are few studies addressing the structure and function of the LGN and visual cortex in MS individuals with and without a history of the optic nerve (Faro et al., 2002).

In a post-mortem study, the distribution of cross-sectional areas of the parvocellular cells in the LGN were found to be significantly smaller for MS, in contrast with healthy controls. However, the same does not seem to be true for the magnocellular cells, where no significant differences were found (Evangelou et al., 2001). Korsholm and colleagues (2007) reported that during an acute episode of optic neuritis, monocular stimulation of the affected eye produced a significant reduced activation, in contrast with the unaffected eye. Additionally, upon recovery,

differences between the affected and unaffected eye on LGN activation diminished and even disappeared 180 days after an acute episode.

Korsholm and colleagues (2007) also described a decreased activation of the visual cortex (V1, V2, and Lateral Occipital Cortex - LOC) in the acute phase of optic neuritis, when stimulating the affected eye in comparison to the unaffected eye. Similarly to what happened with the LGN, with recovery activations on LOC, V1 and V2 no longer differed after 180 days.

Different results were found by Faro and colleagues (2002) who found significant differences between the MS and healthy control group through a luminance paradigm in a functional magnetic resonance imaging (fMRI) study. As expected, both groups presented an increased number of activated voxels as a function of luminance contrast. However, for all the luminance contrast levels, the MS group activated a significant lower number of voxels in the primary visual cortex, when contrasted with the other group. Furthermore, the activation threshold was different for both groups as well. While MS participants reached a significant increase in imaging activation only at the seventh graded level of luminance, healthy controls accomplished this at the second grade level. Authors have claimed that the results might be an expression of a reduction in the number of neurons and a decreased activation in the disease axons along the visual pathways (Faro et al., 2002).

Conclusion

During the course of MS, episodes of neuro-ophthalmic syndromes are frequent, leading to significant visual disturbances during the acute phase. Often total or partial clinical recovery is reached; yet, long-term abnormalities are frequently found, such as RNFL thickness, as well as optic nerve, LGN and visual cortex atrophy, or abnormal primary visual cortex activations. The

degree of severity of these abnormalities seems to be related with a history of neuro-ophthalmic syndromes; nonetheless, such defects might also appear in its absence. Although there is a fair amount of knowledge regarding abnormalities of the visual system in MS, little is known about the possible implications of these anomalies on the performance of MS individuals during vision-based neuropsychological tasks, and more generally in visual processing speed. In the next chapter, I will present a brief overview of the cognitive function in patients with MS.

COGNITIVE FUNCTION IN MULTIPLE SCLEROSIS

A fair amount of research has demonstrated that cognitive impairment in MS individuals is common, and significantly interferes with the person's quality of life and everyday activities. Below, I will present an overview of recent findings concerning overall cognitive function in MS, emphasizing processing speed and visual abnormalities, commonly concomitant with MS.

Neuropsychological function in Multiple Sclerosis

Cognitive impairments is estimated to affect between 43% and 70% of MS patients. The impairments varies remarkably between MS individuals, and can be present during the early or later stages of the disease (Achiron & Barak, 2003; Bagert, Camplair, & Bourdette, 2002). Cognitive deficits have been documented in specific domains, including long-term memory, learning, information-processing speed, verbal fluency, attention and executive function, but commonly spares overall intelligence (Chiaravalloti & DeLuca, 2008; DeLuca & Nocentini, 2011; Genova, Sumowski, Chiaravalloti, Voelbel, & Deluca, 2009b; Magnano, Aiello, & Piras, 2006; Patti, 2009; Prakash et al., 2008). The duration of the disease or the level of disability, measured on the Expanded Disability Status Scale (Kurtzke, 1983), is reported to be a weak predictor of the cognitive performance of the most important neuropsychological measures (Amato, Zipoli, & Portaccio, 2006b; Patti et al., 2009).

Cognitive deficits in individuals with MS significantly affect their everyday activities, job performance, emotional status and social functioning, all of which greatly compromise their overall quality of life (Goverover, Genova, Hillary, & DeLuca, 2007; Kalmar, Gaudino, Moore, Halper, & Deluca, 2008).

Fatigue and depression, two common symptoms in individuals with MS, are believed to interfere with cognitive function as well as with overall quality of life.

Krupp and Elkins (2000), in a study exploring the effects of fatigue on the execution of a sustained working memory test, concluded that MS participants showed diminished performance during the course of the task, measured by higher reaction times, in contrast with healthy controls. Similar results were found by Bryant, et al (2004) in a study using the Paced Auditory Serial Addition Test, where the effect of fatigue on the execution of a continuous working memory task was assessed. Regardless of their cognitive function (impaired or non-impaired), MS participants showed a higher susceptibility to cognitive fatigue, as expressed by fewer correct responses, in contrast with healthy controls.

Some studies suggested a negative relation between high levels of depressive mood and cognitive performance, namely in working memory, processing speed, learning, abstract reasoning and executive functions (Arnett et al., 1999a; Arnett et al., 1999b; Barwick & Arnett, 2011; Demaree, Gaudino, & DeLuca, 2003).

Recently, imaging studies have revealed that participants with a low 'cognitive reserve' might be at particular risk of developing cognitive impairments. Cognitive reserve theories postulate that the intellectual enrichment developed along the person's lifetime attenuates the negative impact of brain pathology on cognitive function (Stern, 2002, 2009). MS participants possessing a higher 'cognitive reserve' were found to be able to withstand more brain pathology before expressing a cognitive performance similar to MS participants with a low 'cognitive reserve' (Sumowski, Chiaravalloti, Wylie, & Deluca, 2009; Sumowski, Wylie, Chiaravalloti, & DeLuca, 2010; Sumowski, Wylie, Deluca, & Chiaravalloti, 2010). Interestingly, a study reported that not all cognitive functions are protected by the 'cognitive reserve'. While

significant positive interactions for complex information processing efficiency as well as for verbal learning and memory were found, the same did not happen in the case of simple processing efficiency (Sumowski, Chiaravalloti, & DeLuca, 2009).

Processing Speed deficit in Multiple Sclerosis

Processing speed has been consistently pointed out as one of the most common deficits in MS (Brassington & Marsh, 1998; Chiaravalloti & DeLuca, 2008; Patti, 2009; Prakash et al., 2008) and there has consequently been a significant increase in the number of studies on this topic in the last decade (De Sonneville et al., 2002; DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Genova, Hillary, Wylie, Rypma, & Deluca, 2009a; Lazeron, de Sonneville, Scheltens, Polman, & Barkhof, 2006). Moreover, processing speed deficits may also impact other cognitive functions such as attention or working memory.

Although all MS profiles present a general slowing down in cognitive processing, these deficits are particularly pervasive in secondary progressive patients, followed by the primary progressive group and finally by that of the relapse-remitting group, which is probably the least affected (De Sonneville et al., 2002; Snyder, Cappelleri, Archibald, & Fisk, 2001).

Theories concerning the neural causes of processing speed deficit

The exact neural cause of processing deficits in MS is still unclear. Nonetheless, some theories have been proposed. Similarities between MS cognitive impairments and subcortical dementias were highlighted by some researchers. As is the case for subcortical dementias, the processing speed in MS is a preeminent deficit, often associated with white-matter pathology (Rao, 1996).

According to Kail (1997), the neural noise hypothesis could provide important insight on the understanding the neural causes of processing speed deficits in MS. The neural noise hypothesis is based on the assumption that within the CNS the information is transmitted in varying degrees of fidelity or strength, against a background of random neural activity or noise (Salthouse & Lichty, 1985). Similar to what happens during the ageing process, Kail (1997, 1998) hypothesized that in MS the signal-to-noise ratio decrease, leading to slower processing speed. In two studies, developed to test the 'neural noise hypothesis' in MS, the author concluded that reaction times (RTs) for MS participants increased linearly as a function of RTs for healthy volunteers, showing a sharp increase for MS participants with more severe symptoms (Kail, 1997, 1998).

As pointed out by Genova and colleagues (2009b), the relation between processing speed and higher order cognition has mostly been studied in the literature on normal ageing. As an example, Salthouse's (1996) theory of "limited time mechanisms" states that the amount of time available to perform later operations is restricted when a large allocation of resources is involved in the execution of prior operations. Taking this theory into consideration, in complex cognitive tasks, the effects of limited time mechanisms will become more apparent, and thus, MS individuals with processing speed deficits would suffer more when compared to a healthy control group.

Some studies with MS participants have reported results validating Salthouse's theory (Leavitt, Lengenfelder, Moore, Chiaravalloti, & DeLuca, 2011; Lengenfelder et al., 2006). In a recent study, Leavitt and colleagues (2011) showed that participants with MS tend to perform differently, depending on how much time is available. As predicted by the theory of "limited time mechanisms" (Salthouse, 1996), MS individuals with processing speed deficits benefited

the most when given extra time (in comparison to MS participants without processing deficits and healthy control groups).

What is processing speed?

Despite the fact that a fair amount of research has been carried out with regard to processing speed, the construct itself was rarely conceptualized, and when it was, it was frequently defined operationally or methodologically as reaction time. Frequent definition confounds rely on the absence of a 'pure' processing speed neuropsychological measure, as well as on the fact that processing speed has been historically conceptualized as a unitary concept (Demaree, Frazier, & Johnson, 2008). This renders the generalization of results and the comparison of studies on processing speed difficult to undertake. Therefore, an accepted working model of human processing speed, which is integrated into larger theories of cognitive operations of the brain, has still not been reached, despite the growing interest in the study of information processing speed in the last 30 years (DeLuca, 2008). DeLuca proposed that processing speed could be defined as *'the time required to execute a cognitive task or the amount of work that can be completed within the finite period of time'* (DeLuca, 2008).

Visual processing in Multiple Sclerosis

Even though the visual system is frequently compromised in MS due to neuro-ophthalmic syndromes (e.g, optic neuritis), there have been few studies addressing the implications of visual deficits on cognitive performance. Visual processing can be understood as the ability to recognize a visual stimulus, as well as the capability to accurately perceive the characteristics of that stimulus (Chiaravalloti & DeLuca, 2008). Even MS individuals with normal or corrected-to-normal visual acuity were found to underperform on visuoperceptual tasks (Vleugels et al.,

2000), as well as in perceptual discrimination and visual object recognition (Genova et al., 2009b; Laatu, Revonsuo, Hamalainen, Ojanen, & Ruutiainen, 2001). Additionally, MS individuals with cognitive impairment often reveal processing difficulties on visual shape recognition and semantic-lexical processing, when compared with MS individuals without cognitive deficits or healthy controls, and even early stages of visual processing (Laatu et al., 2001). Moreover, mild visual acuity disturbances were recently associated with worse performances in visual processing neuropsychological tasks in MS (Bruce, Bruce, & Arnett, 2007; Davis, Hertza, Williams, Gupta, & Ohly, 2009; Feaster & Bruce, 2011).

Neuro-ophthalmic syndromes are frequent during the course of MS, but implications in the performance of vision-based neuropsychological tasks and overall visual processing speed are still elusive.

The remaining chapters

The current thesis aims to contribute to a further understanding of visual processing speed deficits in relapse remitting MS (RRMS) individuals. Specifically, it is our objective to understand whether the history of neuro-ophthalmic syndromes might be related with worse performances in vision-based processing speed tasks (Study I). Additionally, we proposed to study the relation between visual processing speed deficits and the temporal dynamics of visual processing (Study II).

HISTORY OF NEURO-OPHTHALMIC SYNDROMES INTERACTS WITH PROCESSING SPEED IN MULTIPLE SCLEROSIS

Abstract

Multiple sclerosis (MS) is a chronic, neurologic, disabling disease. In the course of MS, episodes of neuro-ophthalmic syndromes are common and frequently lead to long-term abnormalities. Although a fair amount of research has been conducted on cognitive functioning in MS, how the history of neuro-ophthalmic syndromes might affect the performance of MS individuals on vision-based neuropsychological tasks is understudied.

The aim of the current study is to understand whether the history of neuro-ophthalmic syndromes might be related to poor performance on neuropsychological tasks in relapse-remitting MS participants with normal or corrected-to-normal visual acuity.

Our results suggest that a history of neuro-ophthalmic syndromes is related to poor performance on vision-based tasks, specifically those aimed to assess processing speed tasks. We propose that the abnormalities often found in the visual system after neuro-ophthalmic syndromes might give further insights on the visual processing speed deficits frequently found in MS populations.

Introduction

Multiple sclerosis (MS) is a chronic neurologic disabling disease with unpredictable severity and progression. It is estimated that approximately 400,0000 people in the USA and approximately 2.1 million worldwide have MS (DeLuca & Nocentini, 2011). The onset of the disease frequently occurs between the ages of 20 and 40 years old, but it can also affect children or older individuals (Confavreux & Compston, 2007).

It has been well established that individuals with MS are at an increased risk for impairment in a variety of areas (Caramia et al., 2010; Chiaravalloti & DeLuca, 2008; DeLuca & Nocentini, 2011; McDonald & Compston, 2007). Although a fair amount of research has been conducted on cognitive functioning in MS, how the history of neuro-ophthalmic syndromes might affect the performance of MS individuals on vision-based neuropsychological tasks has not been well studied.

Neuro-ophthalmological syndromes in MS

Over the course of MS, acute episodes of neuro-ophthalmological syndromes are common as a result of different disease-related processes, such as inflammation, demyelination and neurodegeneration (Burton et al., 2011). Neuro-ophthalmological syndromes may compromise the afferent visual system (e.g., optic neuritis (Frohman et al., 2008a; Kolappan et al., 2009; McDonald & Barnes, 1992; Shams & Plant, 2009)), and/or the ocular motor system (e.g., nystagmus or internuclear ophthalmoplegia (Barnes & McDonald, 1992; Niestroy et al., 2007; Prasad & Galetta, 2010)). Neuro-ophthalmic syndromes are generally characterized by an abrupt onset with different levels of severity, and recovery is usually reached within weeks after

an acute episode. Although full clinical recovery from acute episodes is commonly achieved, long-term abnormalities in different visual system components have frequently been described (Frohman et al., 2005; Frohman et al., 2010; Maxner, 2006). While visual system abnormalities are strongly associated with a history of acute episodes of neuro-ophthalmic syndromes, they can also be detected in MS individuals without any past history of neuro-ophthalmic syndromes (Fjeldstad et al., 2011; Lycke, Tollesson, & Frisen, 2001; Petzold et al., 2010).

It has been shown, for instance, that individuals with MS present with decreases in retinal nerve fiber layer (RNFL) thickness (Petzold et al., 2010; Talman et al., 2010), optic nerve atrophy (Burton et al., 2011; Trip et al., 2006), and abnormal visual evoked potentials characterized by visual P100 delayed latencies (Almarcegui et al., 2010; Gareau et al., 1999). It has also been reported that MS individuals can present abnormal visual cortex activations (Audoin et al., 2006; Levin, Orlov, Dotan, & Zohary, 2006), or abnormal oculomotor performance (Niestroy et al., 2007; Prasad & Galetta, 2010).

Cognitive functioning in MS is typically assessed using neuropsychological tasks, the interpretation of which may be influenced by several factors, including visual problems. Likewise, a panel of experts composed of both neuropsychologists and psychologists proposed that measures of sensory functions, such as the Rosenbaum Pocket Vision Screener, should be included in evaluation batteries because they would give valuable information for the interpretation of neuropsychological test results (Benedict et al., 2002). Despite the fact that several of the most used neuropsychological tests are vision-based, the impact of visual system abnormalities (frequently associated with a history of neuro-ophthalmic syndromes) in the

performance of MS individuals is still not fully understood.

Neuropsychological aspects of MS

Cognitive impairment is estimated to affect between 43% and 70% of MS patients (Chiaravalloti & DeLuca, 2008; DeLuca & Nocentini, 2011), significantly compromising overall quality of life, everyday activities, job performance, emotional status and social functioning (Goverover et al., 2007; Kalmar et al., 2008).

Although the profiles of cognitive deficits in MS are rather heterogeneous, individuals with MS, independently of their MS progression type, often show impairments in attention, information processing speed and efficiency, episodic memory, executive functions and visuo-perceptual skills, along with generally intact overall intelligence (Amato et al., 2006b; Caramia et al., 2010; Chiaravalloti & DeLuca, 2008; DeLuca & Nocentini, 2011; Magnano et al., 2006; Patti, 2009; Prakash et al., 2008).

The aim of the present study is to explore the extent to which a history of neuro-ophthalmic syndromes might influence performance on common vision-based neuropsychological tests.

Vision and cognition

Despite the fact that both visual abnormalities and cognitive impairment are common in MS, the complex interaction between these two is not completely understood. The few studies that address this relationship found that mild visual acuity deficits (Bruce et al., 2007; Davis et al., 2009; Feaster & Bruce, 2011), as well as abnormal eye movements (Fielding, Kilpatrick, Millist, & White, 2009a, 2009b), were associated with worse cognitive performances.

Mild visual acuity disturbances (acuities greater than or equal to 20/40 on the Snellen near eye chart; Graham-Field, Fond du Lac. WI) were found to be associated with poor performances on visual processing speed tasks and with higher levels of physical disability (Bruce et al., 2007; Davis et al., 2009). Similarly, Feaster and Bruce (2011), concluded that subtle visual impairments were robustly associated with motor and cognitive difficulties as measured by visual and non-visual tasks.

In two studies on the relationship between saccadic eye movements and cognitive performance, Fielding and collaborators (Fielding et al., 2009a, 2009b), concluded that, even in the absence of clinical signs of MS, oculomotor characteristics are a sensitive indicator for evaluating deficits in working memory and inhibitory control processes, as well as attention. Therefore, it is of major importance to explore the implications of mild visual disturbances on vision-based neuropsychological task performance.

The aim of the current study is to understand whether the presence of a history of neuro-ophthalmic syndromes might be related to poor performance on neuropsychological tasks in relapse-remitting MS participants with normal or corrected-to-normal visual acuity. We expect that MS participants with a history of neuro-ophthalmic syndromes will perform worse on vision-based neuropsychological tests, particularly on visual processing speed tasks, than MS participants without such a history and healthy controls.

Methods

Participants

Eighteen individuals with relapse-remitting MS (McDonald et al., 2001) and nine healthy

control subjects participated in the experiments. Before being enrolled in the study, all participants signed a consent form approved by the Institutional Review Board of the Kessler Research Center. All MS participants were right handed (M = 85.24, SEM = 4.08), one healthy control ('HC') was ambidextrous, and the other eight were right-handed (M = 70.6, SEM = 8.26), as measured by the Edinburgh Handedness Inventory (Oldfield, 1971).

All participants were selected such that they did not report any past history of medical or psychiatric disorders that could substantially influence cognitive function or have any lasting impact on brain integrity, including, but not limited to, craniocerebral trauma (with greater than 30 minutes of loss of consciousness), alcohol or drug dependence (past or present), learning disability, bipolar disorder, schizophrenia, or stroke, a relapse within four weeks of testing (for MS participants), or being medicated with steroids, benzodiazepines or neuroleptics.

MS individuals were subdivided into two groups according to their past history of MS-related neuro-ophthalmic syndromes. One group included MS participants with a history of neuro-ophthalmic syndromes (e.g., nystagmus, optic neuritis; henceforth, this group is called 'with history'; N=12), whereas the other group consisted of MS individuals who did not have any history of neuro-ophthalmic syndromes (henceforth called 'without history'; N=6). Participants from the healthy control group did not report any history of visual disturbances. The two MS groups did not differ on the number of months since diagnosis (t (16) = 1.44, n.s.; 'with history' M = 150.75 months, SEM = 30.07, range 19–384 months; and 'without history' M = 85.33 months, SEM = 21.39, range 24–156 months). See Table 2 for a detailed description of demographic information for the three groups.

Differences between groups were assessed with an analysis of variance test (ANOVA), which

revealed that the three groups did not differ in age (F (2,24) = 0.61, n.s.). The 'with history' group had a mean age of 41.75 years old (SEM = 3.2), whereas the 'without history' group had a mean age of 43.67 years old (SEM = 2.8), and the 'HC' group had a mean age of 38.56 years old (SEM = 2.46). An ANOVA also revealed that the three groups did not differed in terms of years of education (F (2,24) = 1.08, n.s.). The 'with history' group had an average of 14.92 (SEM = 0.71) years of education, whereas the 'without history' group had, on average, 14.17 (SEM = 0.65) years of education, and the 'HC' group had 15.78 (SEM = 0.62) years of education.

Additionally, significant differences were found on the Beck Depression Inventory (F (2,23) = 5.25, p = 0.01). The 'HC' group showed lower values of depressive symptomatology (M = 1.67, SEM = 0.78) than both MS groups (M = 11.45, SEM = 2.66 for the 'with history' group; t (11.69) = 3.53, p < 0.01; and M = 9.83, SEM = 3.12 for the 'without history' group; t (5.6) = -2.54, p < 0.05). Furthermore, equal level of depressive symptomatology was observed between the two MS groups (t (15) = 0.38, n.s.).

The Snellen High Contrast Vision Chart was used to measure binocular high-contrast visual acuity. Fractions were recorded for the lowest line that participants could correctly read. The participants were tested with their glasses or contacts, and thus corrected vision was assessed. A binocular Snellen acuity score of less than 20/70 in both eyes, with optical correction, was established as the cut-off point for study enrollment, as this score has been regarded as the minimum visual acuity for neuropsychological testing (McCarthy & Warrington, 1990). ANOVA with the Snellen acuity test scores revealed no significant differences between the three groups for acuities on both eyes (right eye F (2,23) = 0.46, n.s.; left eye F (2,23) =

1.02, n.s.). The mean acuities for the right eye were 20/31.67 (SEM = 3.81) and 20/29.17 (SEM = 4.36) for the 'with history' and 'without history' groups, respectively, and 20/26.88 (SEM = 2.30) for the 'HC' group. Likewise, left eye acuity means for 'with history' and 'without history' were found to be, respectively, 20/44.17 (SEM = 14.39) and 20/28.33 (SEM = 4.59), while the 'HC' group had a mean acuity of 20/22.5 (SEM = 1.89). Overall intelligence was assessed using the Wide Range Achievement Test-Third Edition (WRAT-3) reading subtest, and the results were similar between the three groups (F (2,24) = 2.48, n.s.; 'with history' group, M = 100.33 (SEM = 4.57), 'without history' group M = 100 (SEM = 4.38), and 'HC' group M = 111.78 (SEM = 2.77).

Table 2– Demographic Information for participants

	HC (N=9) M (SEM)	'with history' (N=12) M (SEM)	'without history' (N=6) M (SEM)	F
Age	38.56 (2.46)	41.75 (3.2)	43.67 (2.8)	F (2,24) = 0.61
Years of education	15.78 (0.62)	14.92 (0.71)	14.17 (0.65)	F (2,24) = 1.08
BDI Total	1.67 (0.78)	11.45 (2.66)	9.83 (3.12)	F (2,23) = 5.25**
Acuity Right eye	20/26.88 (2.3)	20/ 31.67 (3.81)	20/ 29.17 (4.3)	F (2,23) = 0.46
Acuity Left eye	20/22.5 (1.89)	20/44.17 (14.39)	20/28.33 (4.59)	F (2,23) = 1.02
WTAR	111.78 (2.77)	100.33 (4.57)	100 (4.38)	F (2,24) = 2.48

Note: BDI Total: total score of the Beck Depression Inventory; Acuity Right eye and Left eye: represent the scores obtained by each participant on the Snellen High Contrast Vision Chart for right and left eye *p<0.05; **p<0.01; ***p<0.001.

Neuropsychological assessment

The neuropsychological evaluation was conducted in one or two sessions and covered five cognitive domains usually compromised in MS (processing speed/working memory, learning and memory, executive function, visual-spatial processing and word retrieval).

To assess cognitive functioning, all participants underwent the Minimal Neuropsychological Assessment of Multiple Sclerosis (MACFIMS; for details see Benedict et al. (2002)), and five subtests of WAIS. MACFIMS (Benedict et al., 2002) is a comprehensive battery often used with MS populations and is composed of six evaluation tests measuring verbal fluency (Control Oral Word Association Test - COWAT), visual perception (Judgment Line Orientation test - JLO), verbal and visuo-spatial learning and memory (California Learning Verbal Test II – CVLT II and Brief Visuosptatial Memory Test Revised – BVMT-R), processing speed (Symbol Digit Modality Test – SDMT and Paced Auditory Serial Addition Test - PASAT), and executive functions (subtest Sorting from the Delis-Kaplan Executive Function System – DKEFS).

Moreover, the letter and number sequence (LNS), and the arithmetic and the digit span (DS) subtests from the Wechsler adult intelligence scale (WAIS) were used to test working memory performance. Furthermore, the coding (CO) and symbol search (SS) subtests of the WAIS were used to assess visual-motor processing speed functioning.

Of the tasks in this comprehensive neuropsychological test battery, six are vision-based, - i.e., they use visual stimuli as their stimuli of interest (JLO, SDMT, DKEFS Sorting, BVMT-R, SS, and CO), and six are auditory-based, as they are performed over auditory stimuli (COWAT, CVLT II, DS, PASAT, LNS, and Arithmetic).

Data analyses

ANOVAs were performed with each neuropsychological task as a within-subject factor and with group (healthy control, 'with history' and 'without history') as a between-subject factor to understand differences in cognitive performance. Post hoc comparisons of the mean values were carried out by independent samples t-tests when the ANOVAs revealed significant effects. Data are presented as the mean (M) and standard error of the mean (SEM). The criterion for statistical significance was established at $p < .05$. All statistical analyses were performed using IBM SPSS Statistics for Mac OS (version 20).

Results

Vision-based neuropsychological tasks

Significant differences between groups were found for the following processing speed tasks: SS ($F(2,24) = 8.24$, $p < 0.01$), SDMT ($F(2,24) = 7.37$, $p < 0,01$), and CO ($F(2,24) = 5.01$, $p < 0.02$). Additionally, a main effect of group was also found for the long-term visual memory task, BVMT-R Delay ($F(2,24) = 3.84$, $p < 0.05$; see Table 3 for a detailed description).

The MS group with a history of neuro-ophthalmic syndromes ('with history') achieved worse performances in comparison with the 'HC' group on SS (M = 9.08, SEM = 0.9, for 'with history' group; and M = 13.89, SEM = 0.77 for 'HC' group; $t(19) = -3.88$ $p < 0.01$), whereas equal performances were obtained for the 'with history' and the other MS group ('without history'; M = 9.83, SEM = 1.08; $t(16) = -0.5$, n.s.). Additionally, the 'without history' group achieved also poor performances on SS in contrast with the 'HC' group ($t(13) = -3.15$, $p <$

0.01).

Concerning the SDMT, the 'with history' group (M = - 1.97, SEM = 0.43) performed worse than the 'HC' (M = - 0.07, SEM = 0.35; t (19) = - 3.29, $p < 0.01$), and the 'without history' groups (M = - 0.35, SEM = 0.29; t (16) = -2.51, $p < 0.03$). Furthermore, no significant difference was found between the 'without history' and the 'HC' groups on SDMT (t (13) = - 0.58, n.s.).

On CO, significant differences were also found between the 'with history' and 'HC' groups (M = 8.00, SEM = 1.19, for 'with history' group; and M = 12.89, SEM= 0.77, for 'HC' group; t (19) = - 3.18, $p < 0.01$). Additionally, no differences were found between the 'without history' group performance on CO (M = 10.50, SEM = 1.48) than the other two groups (t (16) = - 1.26, n.s., for 'with history'; and t (13) = - 1.57, n.s. for 'HC' group).

Similarly, poor performances were obtained on the BVMT-R delay by the 'with history' group (M = -1.57, SEM = 0.43) in contrast with the 'HC' group (M = 0.03; SEM = 0.27; t (17.59) = - 3.13, $p < 0.01$). Finally, the performance of the 'without history' group on BVMT-R Delay (M = - 1.21, SEM = 0.65) was found to be similar to the other MS group ('with history'; t (16) = - 0.47, n.s.), as well as the 'HC' group (t (6.77) = - 1.76, n.s.).

In accordance with the regression based norms proposed by Parmenter, Testa, Schretlen, Weinstock-Guttman, and Benedict (2010), the 'with history' group, on average, demonstrated impairments on the BVMT-R delay and SDMT tests. Although the 'without history' group achieved a much poorer performance on SDMT compared with the 'HC', these results are not clinically significant, since on average results are above the cut-off of a z score -1.5. Therefore, we may conclude that no overall visual processing speed deficit was found for the 'without

history' group.

No differences between groups were found for JLO (F (2,24) = 0.11, n.s.), BVMT-R total learning (F (2,24) = 0.88, n.s.) or the DKEFS Sorting measures (sorting (F (2,24) = 0.57, n.s.) and descriptions (F (2,24) = 1.07, n.s.).

Visual perception (JLO) was found to be similar between the 'with history' (M = 0.56, SEM = 0.31), 'without history' (M = 0.56, SEM = 0.21) and 'HC' groups (M = 0.37, SEM = 0.33). Equal results were achieved for total visuo-spatial learning, as measured with BVMT-R Learning, where the 'with history' (M = -1.39, SEM = 0.35), 'without history' (M = -1.03, SEM = 0.65) and 'HC' (M = -0.66, SEM = 0.36) groups did not differ between each other. Concerning executive functions, from the total scores of the DKEFS Sorting test, the 'with history' (M = - 0.34, SEM = 0.52), 'without history' (M = -0.03, SEM = 0.43) and 'HC' (M = 0.36, SEM = 0.43) groups attained similar results. Finally, for the total description from the DKEFS Sorting test, similar performances were also attained by the three groups: 'with history' (M = - 0.73, SEM = 0.42), 'without history' (M = - 0.76, SEM = 0.28), and 'HC' (M = 0.01, SEM = 0.4

Auditory-based neuropsychological tasks

There was a significant main effect of group for LNS (F (2,24) = 8.77, $p < 0.01$) and DS (F (2,24) = 3.69, $p < 0.05$). The 'with history' group performance worse on the LNS (M = 9.33, SEM = 0.53) than the 'HC' group (M = 13.11, SEM = 0.87; t (19) = - 3.9, $p < 0.01$), but did not differ from the 'without history' group (M = 10.17, SEM = 0.65; t (16) = - 0.95, n.s.). Additionally, the 'without history' group also achieved significantly lower scores on LNS than

the 'HC' group (t(13) = 2.45, p<0.03).

Concerning DS, a significant difference was found between 'with history' (M = 9.58, SEM = 0.79), and 'HC' groups (M = 12.78, SEM = 1.16; t(19) = - 2.35, p = 0.03). Additionally, the 'without history' group (M = 9.67, SEM = 0.71) attained similar results as the 'with history' (t(16) = - 0.07, n.s.), and the 'HC' (t(13) = 2.00, n.s.).

Furthermore, there was no significant effect of group for COWAT (F(2,24) = 0.2, n.s.), CVLT II total learning (F(2,24) = 1.41, n.s.), CVLT II delay recall (F(2,24) = 1.72, ns), PASAT (F(2,24) = 0.13, ns), or arithmetic (F(2,24) = 1.26, n.s.).

The three groups did not differ on verbal fluency as measured by COWAT ('with history' M = -0.58, SEM = 0.43; 'without history' M = -0.59, SEM = 0.18; and 'HC' M = -0.30, SEM = 0.23). Regarding verbal learning, the results show that the three groups performed the CVLT II learning task ('with history' M = -0.86, SEM = 0.41; 'without history' M = -0.18, SEM = 0.46; and 'HC' M = -0.03, SEM = 0.26) and CVLT II delay recall ('with history' M = -0.76, SEM = 0.43; 'without history' M = -0.54, SEM = 0.37; and 'HC' M = 0.17, SEM = 0.23) without significant differences. Likewise, there were no differences in performance between the three groups for auditory processing speed, as measured with the PASAT ('with history' M = 8.5, SEM = 0.89; 'without history' M = 8.5, SEM = 0.56; and 'HC' M = 10.33, SEM = 1.04). Finally, arithmetic ability was found to be similar between the 'with history' (M = 8.5, SEM = 0.89), 'without history' (M = 8.5, SEM = 0.56) and 'HC' groups (M = 10.33, SEM = 1.04).

Table 3 – Neuropsychological Evaluation Results

	Healthy Controls (*N*=9) M (SE)	'with history' (*N*=12) M (SE)	'without history' (*N*=6) M (SE)	*F*(2,24)
COWAT (Z score) [b]	-0.30 (0.23)	-0.58 (0.43)	-0.59 (0.18)	0.20
JLO (Z score) [a]	0.37 (0.33)	0.56 (0.31)	0.56 (0.21)	0.11
CVLT II Total learning (Z score) [b]	-0.03 (0.26)	-0.86 (0.41)	-0.18 (0.46)	1.41
CVLT II Free Delay Recall (Z score) [b]	0.17 (0.23)	-0.76 (0.43)	-0.54 (0.37)	1.72
BVMTR Total Learning (Z score) [a]	-0.66 (0.36)	-1.39 (0.35)	-1.03 (0.65)	0.88
BVMTR Total Delay Recall (Z score) [a]	0.03 (0.27)	-1.57 (0.43)	-1.21 (0.65)	3.84[*, i]
SDMT (Z score) [a]	-0.07 (0.35)	-1.97 (0.43)	-0.35 (0.29)	7.37[**, i; ii]
PASAT 3'' (Z score) [b]	0.08 (0.49)	-0.22 (0.50)	0.09 (0.44)	0.13
D-KEFS Total Sorting (Z score) [a]	0.36 (0.43)	-0.34 (0.52)	-0.03 (0.43)	0.57
D-KEFS Total Description (Z score) [a]	0.01 (0.4)	-0.73 (0.42)	-0.76 (0.28)	1.07
Letter-Number Sequence (WAIS) (Scale score) [b]	13.11 (0.87)	9.33 (0.53)	10.67 (0.65)	8.77[***, i; iii]
Arithmetic (WAIS) [b] (Scale score)	10.33 (1.04)	8.5 (0.89)	8.5 (0.56)	1.26
Digit Span (WAIS) (Scale score) [b]	12.78 (1.16)	9.58 (0.79)	9.67 (0.71)	3.69[*, i]
Symbol Search (WAIS) (Scale score) [a]	13.89 (0.77)	9.08 (0.9)	9.83 (1.08)	8.24[**, i; iii]
Coding (WAIS) (Scale score) [a]	12.89 (0.77)	8.00 (1.19)	10.50 (1.48)	5.01[*, i]

Note: COWAT: Control Word Association Test; JLO: Judgment Line Orientation; CVLT-II: California Learning Verbal Tes II; BVMT-R: Brief Visuosptatial Memory Test – Revised; SDMT: Symbol Digit Modality Test; D-KEFS: Delis-Kaplan Executive Function System. [a] - vision-based neuropsychological test; [b] - auditory-based neuropsychological test. [i] - a significant difference was found between 'with history' and 'HC' groups; [ii] - 'with history' significantly differ from 'without history'; [iii] - differences between 'without history' and 'HC' groups; [*] $p<0.05$; [**] $p<0.01$; [***] $p<0.001$.

Discussion

Although neuro-ophthalmic syndromes are frequent in MS, as far as we know, this is the first study to address their relationship with performance on vision- and auditory-based neuropsychological tasks. A history of neuro-ophthalmic syndromes was found to be significantly correlated with poor performances in visual processing speed and auditory working memory.

Performance on vision-based neuropsychological tests seems to be differentially influenced by the history of neuro-ophthalmic syndromes. On the one hand, a history of neuro-ophthalmic syndromes seems to be associated with poor performance on all vision-based processing speed tasks in comparison with the healthy control group (SS, Coding and SDMT). On the other hand, similar results between groups were achieved for almost all vision-based tasks where individuals have unlimited time to accomplished the task (JLO, BVMT-R learning and DKEFS Sorting). The only exception was for BVMT-R delay recall, where a significant difference between the healthy control and 'with history' groups was found. It is then possible to conclude that neuro-ophthalmic syndromes are strongly associated with impairments in visual processing speed, but with a preserved capability for processing/performing visual tasks.

MS individuals with a history of neuro-ophthalmic syndromes showed a different pattern of performance than MS individuals without a history of neuro-ophthalmic syndromes, suggesting that the results herein cannot be attributed exclusively to the fact the individuals in the 'with history' group suffer from MS; that is, the results obtained seem to be strongly related with the occurrence of neuro-ophthalmic syndromes.

Visual processing speed impairments in MS might be related to abnormalities within the visual system as a result of neuro-ophthalmic syndromes. Neuro-ophthalmic syndromes frequently lead to abnormalities such as RNFL thickness, optic nerve and lateral geniculate nucleus atrophy or abnormal patterns of visual cortex activation (Frohman et al., 2005; Frohman et al., 2010). Although similar compromises, such as reduced RNFL, were also found in the eyes of MS patients without any history of acute episodes of neuro-ophthalmic syndromes, the level of severity is significantly lower in contrast to the eyes of MS individuals with a history of acute episodes (Petzold et al., 2010). Despite the fact that neuro-ophthalmic syndromes are strongly associated with long-term abnormalities in the visual system, the recovery of visual ability is frequently achieved. In fact, our groups did not differ in terms of their visual acuity, suggesting that participants with a history of neuro-ophthalmic syndromes express a level vision functioning similar to the other two groups. Additionally, deficits were not found for overall vision-based tasks. The three groups demonstrated that they did not differ in their ability to process visual information; nonetheless, when evaluating the speed of visual processing, possible abnormalities within the visual system seem to interfere significantly.

In accordance with the aforementioned hypothesis, SDMT, a well-known vision-based test that measures processing speed, was recently found to be positively correlated with the average and temporal quadrant RNFL thickness, as measured by OCT after controlling for age and number of school years (Toledo et al., 2008). Unfortunately, no results were found concerning the relationship between a history of neuro-ophthalmic syndromes, RNFL thickness and cognitive performance (Toledo et al., 2008).

Delay of visual processing after acute optic neuritis, one of the most common neuro-

ophthalmic syndromes, has been demonstrated with event related potential studies. Visual evoked potential studies showed that abnormal visual P100 latencies are frequent after acute optic neuritis (Almarcegui et al., 2010; Gareau et al., 1999). During acute optic neuritis episodes, significant reductions in both amplitudes and latencies were found. With recovery, amplitudes tended to normalize, whereas latencies often remained compromised. In addition, previous studies suggested that delayed latencies could be associated with demyelination processes (Burton et al., 2011). The higher P100 latency is likely an expression of a delay in processing, thus supporting our hypothesis that, after an acute episode of a neuro-ophthalmic syndrome, abnormalities within the visual system might slow the processing of visual information.

The processes of inflammation, demyelination and neurodegeneration (Burton et al., 2011), which are frequently associated with neuro-ophthalmic syndromes, may be related to abnormal visual system functioning. If neuronal conduction is reduced or temporally dispersed (as proposed by several studies, e.g.Almarcegui et al., 2010; Gareau et al., 1999; Kolappan et al., 2009), the visual system might still be able to process visual information, albeit in a compromised fashion. Our results suggest that, after recovering from neuro-ophthalmic syndromes, participants are still able to appropriately process visual information, but with significant delays; that is, because the speed of processing visual information is slowed, participants will need longer amounts of time to process the same quantity of information as healthy controls or individuals without a history of neuro-ophthalmic syndromes.

Neuropsychological studies have demonstrated that providing extra time to MS individuals with impaired processing speed significantly improves their performance (Demaree, DeLuca,

Gaudino, & Diamond, 1999; Leavitt et al., 2011; Lengenfelder et al., 2006). In a recent study, Leavitt and colleagues (2011) demonstrated that, when given extra time to complete a complex working memory task, MS participants with processing speed deficits significantly improved their accuracy. These results validate the Salthouse theory of the 'limited time mechanism' (Salthouse, 1996). According to this theory, the amount of time available to perform later operations is restricted when a large allocation of resources is involved in the execution of prior operations.

The results found are not expected to be related to visual acuity abnormalities, as reported by past research (Bruce et al., 2007; Davis et al., 2009; Feaster & Bruce, 2011), because the three groups did not differ on the Snellen High Contrast Vision Chart.

Some authors have claimed that important insights about MS pathophysiology, disease progression and severity, and neurodegeneration might easily be assessed from the analysis of different components of the visual system (Burton et al., 2011; Frohman et al., 2008a; Frohman et al., 2008b; Siger et al., 2008; Trip et al., 2006). In actuality, measures such as RFNL thickness or optic nerve atrophy have been consistently correlated with measures of disability, such as brain atrophy (Siger et al., 2008), disease type (Pulicken et al., 2007), physical and cognitive defects (Toledo et al., 2008), and even with neurodegeneration (Burton et al., 2011; Siger et al., 2008).

Despite the fact that processing speed has been defined as one of the most common cognitive deficits in MS and is significantly related with an overall poor quality of life (DeLuca & Nocentini, 2011), the neural causes of processing speed deficits are still under debate.

The present study is, as far as we know, the first to associate visual processing speed abnormalities with a history of neuro-ophthalmic syndromes. We propose that the abnormalities often found in the visual system after neuro-ophthalmic syndromes might give further insights about the visual processing speed deficits frequently registered in MS populations. Our study results suggest that a history of neuro-ophthalmic syndromes is related to poor performance on vision-based processing speed tasks. Because long-term abnormalities often occur after this clinical event, we hypothesized that visual system defects might contribute to the visual processing speed deficits commonly found in MS. This relationship suggests that processing speed impairments, which are often correlated with MS, might be related to a limitation of the visual system in processing visual information with adequate speed.

As noted by previous studies (Bruce et al., 2007; Davis et al., 2009; Feaster & Bruce, 2011), visual disturbances should be of particular interest to neuropsychologists due to the obvious impacts of such impairments on formal assessment measures.

In future research, it would be interesting to determine whether different neuro-ophthalmic syndromes in MS present with different profiles of cognitive performances. Moreover, longitudinal studies might be of interest in understanding the implications of acute stages and subsequent long-term recovery on cognitive function, especially on vision-based neuropsychological tasks.

PSYCHOPHYSICAL ASSESSMENT OF PROCESSING SPEED DEFICITS IN MULTIPLE SCLEROSIS

Abstract

Multiple Sclerosis (MS) is a neurologic disease affecting motoric, cognitive and emotional functioning. Although the integrity of the visual system is often affected in MS, the potential relationship between visual system functioning and cognitive performance is not fully understood.

With the present study, we aim at understanding how putative abnormal temporal properties of visual processing might be related to cognitive deficits. To explore the temporal dynamics of visual processing in MS, we used three well-known psychophysical paradigms: prior-entry (PE), metacontrast masking (MCM), and rapid serial visual presentations (RSVP).

Processing speed deficits, as defined through the use of traditional neuropsychological testing, were associated with a decreased capability to detect visual stimuli and a higher limitation in the temporal processing capacity. Moreover, the average temporal dynamics of visual processing appear to be compromised for participants with MS, independently from cognitive performance.

These results might be an expression of a latent sensorial temporal limitation of the visual system in participants suffering from relapse-remitting MS and perhaps contribute significantly to the observed processing speed deficits. The potential neural causes for the presented results will be discussed.

Introduction

Multiple sclerosis (MS) is an inflammatory, progressive disease of the central nervous system that typically affects adults between 20 and 50 years old (Kornek & Lassmann, 2003). Deficits in cognitive function, motor abilities, vision, psychiatric problems, etc., are frequent and significantly compromise the overall quality of life and performance in daily activities (Chiaravalloti & DeLuca, 2008; DeLuca & Nocentini, 2011).

During the course of MS, acute episodes of neuro-ophthalmic syndromes are common. The clinical manifestations of neuro-ophthalmic syndromes vary in accordance to the component of the visual system that is involved. For instance, Acute episodes of inflammation and demyelination may affect the afferent, (e.g. optic neuritis; McDonald & Barnes, 1992; Shams & Plant, 2009), or efferent visual systems (e.g. nystagmus; Barnes & McDonald, 1992; Prasad & Galetta, 2010). Acute episodes can be characterized by the abrupt onset of visual abnormalities that are often associated with other symptomatology such as pain.

Although clinical recovery is frequently achieved, studies have been demonstrating that long-term defects remain throughout the visual system, (for a review please see Frohman et al., 2005; Frohman et al., 2010; Maxner, 2006; Petzold et al., 2010). Furthermore, studies suggest that in MS, visual system abnormalities may also appear without a history of neuro-ophthalmic syndromes, although in a lower degree (Fjeldstad et al., 2011; Lycke et al., 2001; Petzold et al., 2010). It is still not fully understood, however, what are the implications of these deficits within the visual system on cognitive functions under MS, and specifically on processing speed deficits that are often present in MS (for a detailed discussion please see the previous chapter).

We hypothesize that processing speed deficits in MS may be associated with a sensorial temporal limitation of the visual system. With the present study, we aim at understanding how putative abnormal temporal properties of visual processing might be related to processing speed deficits. With this objective, we will study two different groups of individuals with MS: the first group comprises individuals identified with processing speed deficits and a second preserved group. A group of healthy volunteers will be added as a control group.

The temporal dynamics of visual processing

Before perceiving or responding to a visually presented stimulus, the brain performs a series of complex and dynamic processes, which occur in sequential stages (Duangudom, Francis, & Herzog, 2007; Ramachandran & Cobb, 1995).

The processing of visual information has been studied in normal individuals using careful psychophysics manipulations. Psychophysical studies aim at exploring psychological states and measure the observer's response to a task. The stimuli are carefully manipulated to only target the specific perceptual processes of interest. For instance, Thorpe, Fize, and Marlot (1996) have used a psychophysical manipulation to study the temporal characteristic of visual processing and demonstrated that the detection of a particular class of objects (with some evolutionary interest) in a complex visual scene can be processed as quickly as 150 ms in normal individuals. In our study we employed three psychophysical paradigms in order to understand the temporal dynamics of visual information processing in MS. Below we will introduce the three methodologies: prior-entry, metacontrast masking and repetitive serial visual presentation (RSVP).

Prior-entry

The cognitive system has to be able to prioritize what is relevant over what is irrelevant in order to function optimally (Olivers & Meeter, 2008). Prior-entry theory postulates that information processing might be facilitated by attentional mechanisms: attending to a stimulus accelerates the sensory processing of that stimulus and reduces the time necessary to perceive it (Schneider & Bavelier, 2003; Spence & Parise, 2010).

Prior-entry has been studied with paradigms using pairs of simple stimuli whose onset is asynchronous. Temporal order judgment (TOJ) and simultaneity judgment (SJ) have been the two most commonly used tasks to assess the effects of attention on temporal perception (Schneider & Bavelier, 2003; Spence, Shore, & Klein, 2001). In both tasks, stimulus onset asynchrony (SOA) between the two target stimuli varies using the method of constant stimuli or another adaptive procedure (Spence & Parise, 2010). In a typical TOJ task, participants are asked to report the stimulus that appears first (or second), whereas in SJ tasks (for example Shore, Spence, & Klein, 2001) participants must report whether the two stimuli were presented simultaneously.

Rorden, Mattingley, Karnath, and Driver (1997) used a temporal order judgment task, a simpler version of the one used by Stelmach and Herdman (1991) in order to study visual extinction in patients suffering from lesions on the right temporoparietal regions. With this task, the authors were able to precisely determine whether visual awareness itself was delayed for contralesional events that were competing for attention with the ipsilesional events (Rorden et al., 1997). These authors demonstrated that patients with right temporoparietal lesions suffer from a severe bias to the right, thereafter affecting the time-course of visual awareness (Rorden et al., 1997).

In the present study, we will implement the prior-entry procedure, as proposed by Rorden et al. (1997), to understand whether processing speed deficits in MS are related to abnormalities in the ability to detect and process visual information. We hypothesized that the performance of both MS groups will be similar to the healthy control ('HC') group when the two stimuli are presented at the same time, which suggests an appropriate perception of simultaneity; namely, no preferential response ('right-then-left' or 'left-then-right') when the stimuli are presented simultaneously. Furthermore, if processing deficits are associated with an abnormal capability to detect and process visual information, as we hypothesize, participants with processing speed deficits will require longer SOA between the two stimuli to accurately perceived which one appeared initially compared to the remaining two groups.

Metacontrast masking

The temporal dynamics of visual perception have been widely investigated with visual masking (Breitmeyer, 2007; Breitmeyer & Ogmen, 2000). Metacontrast masking is one of the most used visual masking procedures, in which the mask and target are spatially adjacent (Schwartz, 2004).

In this procedure, the visibility of one stimulus, called the target, is manipulated by presenting another stimulus, the mask, in an adjacent spatial location shortly after (Breitmeyer & Ogmen, 2000). The time between the target and mask, the stimulus onset asynchrony (SOA), is manipulated so that the processing of the target is interrupted by the displayed mask before the target has been fully processed (Norton, Corliss, & Bailey, 2002). Performance improves with longer SOAs, whereas the worst performance or higher mask interference is observed for intermediate SOAs between the target and mask.

These spatiotemporal interactions have provided important information regarding the mechanisms of the visual system, offering further insights regarding the time required to form a percept, and the interactions between objects and visual processes that extend beyond conscious awareness (Duangudom et al., 2007; Enns & Di Lollo, 2000).

According to low-level visual processing theories, during the optimal masking time window, the mask interrupts the ongoing early visual processing of the target and can thus inhibit the target from entering conscious awareness (Breitmeyer & Ogmen, 2000). However, recent studies suggested that the mechanisms operating to produce metacontrast masking might be more complex then what theories of low-level visual processing postulated. Complex interactions between high-level visual processes, such as selective attention, and masking have been recently observed (Boyer & Ro, 2007; Enns & Di Lollo, 2000). Breitmeyer and colleagues (Breitmeyer, 1984) have argued that the metacontrast effects are the result of inhibitory interactions between neurons that represent the contours of the target and mask. The onset of the shapes would initiate neural activity in two channels: one fast acting but short-lived and the other slower-acting although longer lasting. Whereas the first channel would transmit transient events that signal the stimulus on- and offset, the second channel would be responsible for transmitting sustained signals regarding the stimulus shape and color. The metacontrast effects appear when fast-acting signals activated by the mask inhibit the sustained activity generated by the earliest target (Enns & Di Lollo, 2000).

Because the masking effects diminish as the spatial separation between the target and mask increases, it might be the case that the target and mask activate an identical population of retinal or cortical neurons, with receptive fields located near one another. This would cause the masking effect. Longer SOAs between the target and mask activate separate populations of

neurons, and as a result, the target signal does not have to compete with the mask response to be detected (Norton et al., 2002).

To study the dynamics of visual processing in MS, we will use metacontrast masking as proposed by Vorberg, Mattler, Heinecke, Schmidt, and Schwarzbach (2003). The objective is to analyze target detection as a function of the time between the onset of the target and mask. If the capacity to detect and recognize stimuli is related to the putative speed of processing deficits, then we should observe a shift in the performance for MS patients in their capacity to overcome the masking effects compared to both MS participants without processing speed deficits and control participants. We hypothesized that MS participants with processing speed deficits will require higher intervals between the target and mask to obtain identical accuracy as the remaining two groups, thus revealing a delay in the processing of visual information.

Rapid serial visual presentation

We can quickly and accurately recognize briefly flashed stimuli (Thorpe et al., 1996). Nevertheless, temporal processing capacity is limited, and visual recognition can become severely compromised at fast presentation rates (McKeeff, Remus, & Tong, 2007). Object identification might be reliably obtained at moderate presentations rates of ~8-10 items/second (McMains & Somers, 2004), and basic visual changes involving flickers or motions can be detected as fast as 30-50 Hz (Kelly, 1961).

Studies have used Rapid Serial Visual Presentation (RSVP) to estimate the rate at which the visual system can process series of objects. In RSVP tasks, participants typically view two targets before the experiment and then must report which of the two possible targets appeared

in an RSVP stimuli sequence (McKeeff, McGugin, Tong, & Gauthier, 2010; McKeeff et al., 2007; Meng & Potter, 2008; Potter, 1975; Potter & Levy, 1969).

Behavioral studies using RSVP within populations of healthy adults with normal or corrected-to-normal visual acuity, consistently report that visual recognition begins to fail at presentations of ~8–10 items/second and declines sharply at faster presentation rates (McKeeff et al., 2007; McMains & Somers, 2004; Potter, 1975).

These results might be a reflection of a fundamental limitation in the processing capacity of the visual system. According with McKeeff and colleagues (2007), this capacity-limited processing occurs at high-level neural areas, in which the global shapes of objects are encoded. Rapid presentation rates were observed to be associated with peak activities in the areas V1 to V3, intermediate rates with increased activity in area V4, and finally, more anterior areas such as the fusiform face area (FFA) and parahippocampal place area (PPA) peaked at the slowest presentation rates. These results suggested that as visual information is transferred from early to higher visual areas, a progressive decrease in sensitivity to high temporal rates might occur alongside a continuing shift in peak sensitivity toward lower temporal rates (McKeeff et al., 2007).

We will implement the RSVP task, as proposed by McKeeff et al. (2007), to investigate the temporal processing capacity in MS. More specifically, we want to understand whether potential limitations in the processing capacity might be related to processing speed deficits. We hypothesize that MS participants with processing speed deficits will show higher processing speed limitations, namely, a steeper decline in the ability to recognize a visual stimulus as a function of the presentation rate, compared to the remaining two groups.

Methods

Participants

The present study was performed with the sample described in the previous chapter. Eighteen individuals with clinically definite relapse-remitting MS (McDonald et al. 2001) and nine healthy control ('HC') subjects participated in the experiments. Before enrollment in the study, all participants signed a consent form approved by the Institutional Review Board of the Kessler Research Center (for more demographic information and inclusion and exclusion criteria, please see previous chapter).

MS individuals were subdivided into two groups according to their performance on a measure of processing speed (the oral version of the Symbol Digit Modality Test, SDMT (Smith, A. 1982)). The SDMT, as previously reported by other studies (Benedict et al., 2008; Brochet et al., 2008; Drake et al., 2010), is accepted to be a vision-based processing speed test sensitive to the detection of cognitive dysfunction in MS. MS participants that scored one-and-a-half standard deviations below the mean (oral norms of the SDMT obtained from Parmenter et al. (2010)) were included in the processing speed impaired group ('Processing speed impaired'; N = 9; 50%), whereas the other MS participants were included in the unimpaired group ('Processing speed unimpaired'; N = 9; 50). As expected, performance on the SDMT for the three groups was statistically different (F (2,24) = 21.03; $p < 0.001$). Individuals belonging to the processing speed impaired group performed worse than the unimpaired group (Mean for the processing speed of the impaired group = -2.61, SEM = 0.31; Mean for the unimpaired group = - 0.25, SEM = 0.26; t (16) = - 5.77, $p < 0.001$), and the control group (Mean for the

healthy control group = - 0.07, SEM = 0.35; t (16) = 5.46, $p < 0.001$). Equal results were obtained on SDMT by the unimpaired and healthy control groups (t (16) = 0.42, n.s.).

All participants were assessed in a number of control variables to ascertain that they differed only in their processing speed capacity (see table 4 for details). The three groups did not differ in their capacity to perform visual tasks (as assessed by the Judgment Line Orientation Test; F (2,24) = 0.93; n.s.), and in their overall intelligence (as assessed by the reading subtest from the Wide Range Achievement Test-III; Wilkinson, 1993; F (2,24) = 2.82, n.s.). Moreover, the three groups were matched in age (F (2,24) = 1.65, n.s.) and years of education (F (2,24)= 0.84, n.s.), The Snellen High Contrast Vision Chart test revealed no significant differences between the groups for either eye (right eye F (2,23) = 1.206, n.s.; left eye F (2,23) = 1.839, n.s.).

A history of visual disturbance episodes was orally reported by 100% of participants in the processing speed impaired group, and 33.33% of the participants in the unimpaired group. The participants from the HC group did not report any history of visual disturbances. No association was observed for eye acuity and a history of visual disturbances (χ^2 (6) = 6.96, n.s.; and χ^2 (6) = 5.121, n.s.; for the left and right eyes, respectively). Finally, the two MS groups did not differ in the number of months after diagnose (t (16) = -0.3, n.s.).

Table 4 – Demographic Information for participants

	PS impaired (*N*=9) Mean (SE)	PS unimpaired (*N*=9) Mean (SE)	Healthy controls (*N*=9) Mean (SE)	*F*
SDMT	- 2.61 (0.31)	- 0.25 (0.26)	- 0.07 (0.35)	$F(2,24) = 21.03$ ***
JLO	0.28 (0.34)	0.83 (0.23)	0.37 (0.33)	$F(2,24) = 0.93$
WTAR	98 (5.87)	102.44 (3.24)	111.78 (2.77)	$F(2,24) = 2.8$
Age	39.33(3.80)	45.44(2.33)	38.56(2.46)	$F(2,24) = 1.65$
Years of education	14.78(0.88)	14.56(0.60)	15.78(0.62)	$F(2,24) = 0.84$
Acuity Left eye	47.78/20 (19.15)	30/20 (4)	22.5/20 (1.89)	$F(2,23) = 1.839$
Acuity Right eye	26.67/20 (1.44)	35/20 (5.34)	26.88/20 (2.3)	$F(2,23) = 1.206$

Note: Means; standard erro in parenthesis. MS= Multiple Sclerosis. PSD= processing speed deficit. WRAT-3= Wide Range Achievement Test – Third Edition. BDI= Beck Depression Inventory *p<0.05; **p<0.01; ***p<0.001

Experiment A: Prior-entry

Objectives

We will use a temporal order judgment task, as proposed by Rorden and colleagues (1997) as our prior-entry procedure. If detection and processing of visual information is compromised in MS patients with processing speed deficits, as hypothesized, the processing speed impaired group will require a longer SOA than the other groups to achieve the same level of accuracy. Interestingly, this procedure provides a direct index of the potential delays in the detection of

visual stimuli without any motoric confounds that normally result from speeded response procedures.

Apparatus and procedures

In this task, participants were presented with two bars (one to the left and one to the right of fixation at the identical eccentricity) and were asked to report which bar appeared first using a motor response. The temporal lag between the presentations of the two bars was manipulated so that the bars could be presented simultaneously or asynchronously. SOA varied between 0 and 250 ms, in temporal steps of 0, 20, 30, 50, 120, 180, and 250 ms.

The trial sequence was as follows (see Figure 1 for details): Initially, a fixation cross in the center of the screen was presented for 30 ms. The first bar was then presented on the screen with the presentation of the second bar dependent on the particular SOA condition of each trial. Participants were instructed to press a key to indicate which bar was presented first. The bars remaining on the screen until a response was obtained. The experiment consisted of two blocks of 260 trials. Each block was composed of twenty repetitions of six right-bar-first SOAs and six left-bar-first SOAs, in addition to twenty trials with zero SOA (i.e., both stimuli are presented simultaneously). A break was provided between the first and second blocks to withstand the potential negative effects of fatigue on performance. Participants were instructed to guess when uncertain, and although their responses were not timed, they were advised to respond as quickly as possible while maintaining maximum accuracy.

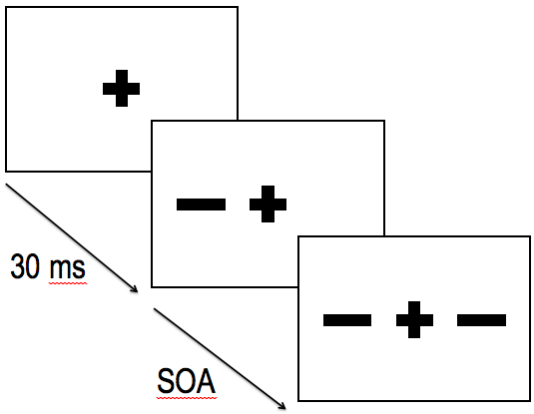

Figure 1 Prior-entry procedure - a base-line fixation cross of 30ms duration started each run. The first bar then appeared, on the left or right side of fixation cross. Second bar appeared

Data analyses

Accuracy was measured and evaluated as a function of the percentage of correct responses by SOA for each participant.

We calculated the minimal SOA required to obtain 75% correct performance per each individual as a function of SOA, by fitting a probit function to the accuracy scores. The threshold (75%) in this study was obtained as a midway value between chance (50%) and maximal performance (100%). We also calculated the slope of the fitted psychometric curve per each individual. The slope of the psychometric curve would be related with the steepness of the increase in the detection performance as a function of SOA.

We used planned contrasts to analyze threshold and slope scores (Rosenthal, Rosnow, & Rubin, 2000) to test the ability of MS participants to detect and process visual information. We performed independent t-tests to contrast the three groups on the minimal SOA needed to achieve 75% accuracy, and on the values of the slope of the psychometric curve.

To control for spurious effects we also performed a series of ANOVAs. A three (group) by two (first and second blocks) repeated measure ANOVA was performed to understand whether the performance of the groups was equal during the two blocks of the experiment, to analyze the potential confounding effects of fatigue during the experiment. A mixed factor analysis of variance (ANOVA) was performed over the accuracy data to test whether the location of the stimulus influenced the responses. When the assumption of sphericity was not met, the Greenhouse-Geisser correction was applied to the degrees of freedom with the corrected probabilities reported. Post-hoc analyses were performed when the main effects and interactions were significant using paired multiple comparisons in the Bonferroni test.

The criterion for statistical significance was established at $p < 0.05$. The mean (M) and standard error of mean (SEM) will be presented for all variables. All statistical analyses were performed with PASW for Mac (version 20).

Results

The results showed main effects of SOA ($F(3.65, 87.63) = 267.9$, $p < 0.001$, $\eta_p^2 = 0.92$) and group ($F(2,24) = 3.57$, $p < 0.05$, $\eta_p^2 = 0.23$) but no significant effect of localization ($F(1,24) = 0.03$, n.s., $\eta_p^2 = 0.01$). Moreover, there was no significant interaction between group, SOA and localization ($F(3.77,45.19) = .13$, n.s., $\eta_p^2 = 0.01$). Performance was influenced by SOA and group, as expected, but not by the location of the first bar. Because temporal order judgments were not significantly influenced by the location of the first bar (left or right), we collapsed the two conditions.

75% threshold analyses

Planned contrast analyses demonstrated that the processing speed impaired group required longer SOAs to detect which bar appeared first with an accuracy of 75% (M = 149.53 ms, SEM = 25.56) compared to the unimpaired group (M = 80.9 ms, SEM = 13.21; t (16) = 2.39, p = 0.03). Similar results were also observed for the processing speed impaired group compared to the HC group (M = 71.83 ms, SEM = 7.53; t (9.378) = 2.916, p < 0.02). Finally, the processing speed unimpaired group typically showed similar results to the HC group (t (16 = 0.596, n.s.; see Figure 2).

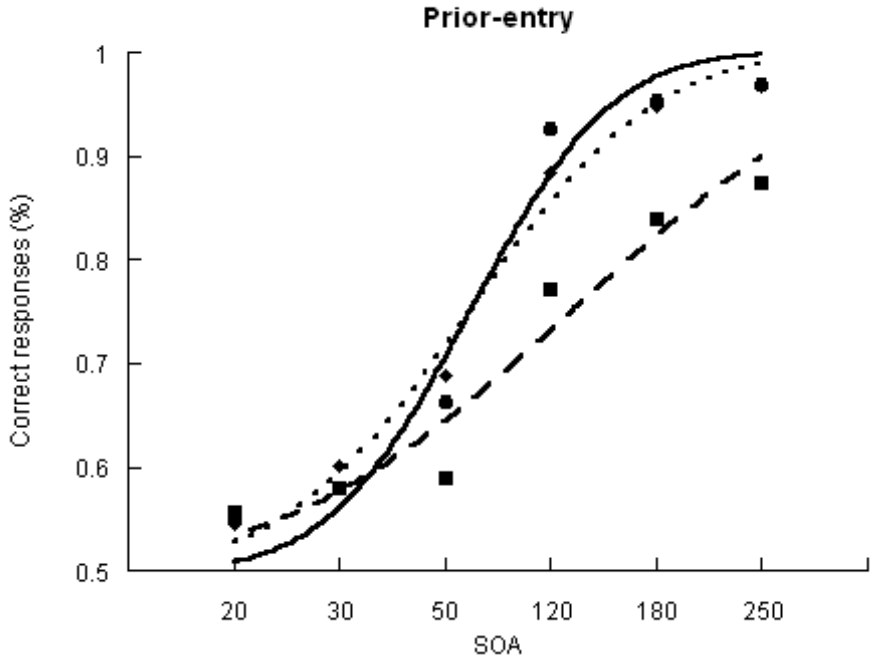

Figure 2 Prior-entry – In this figure, we plotted percent correct performance as a function of SOA. Actual data from the impaired group, non-impaired group and HC group are presented as a filled square (■), a filled diamond (◆), and a filled circle (●), respectively. Lines correspond to fitted data using the probit function. Full Line corresponds to fitted data from the Healthy control group. The Dotted line corresponds to fitted data from the MS processing speed not impaired group. The Dashed line corresponds to fitted data from the MS processing speed impaired group.

Slope of the fitted psychometric curve

In general, the processing speed impaired group obtained a significantly different psychophysics curve slope (M = 0.01, SEM = 0.002) compared to the unimpaired (M = 0.016, SEM = 0.002; t (16) = -2.11, p = 0.05) and HC group (M = 0.023, SEM = 0.005: t (10.825) = -2.545, p = 0.028). The psychophysics slopes for the MS processing speed unimpaired group and HC were not significantly different (t (10.322) = -1.45, n.s.).

The psychophysical curve demonstrated a good fit to the data (MS processing speed impaired group r = 0.92; SEM = 0.03; 0.72 – 0.99; MS processing speed unimpaired group r = 0.98; SEM = 0.01; 0.92 – 1.00; and HC r = 0.98; SEM = 0.01; 0.92 – 1.00).

The 80, 85, and 90% thresholds

To understand how accuracy levels increased as a function of SOA for the three groups, we used planned contrast analyses over the minimal SOAs necessary to achieve 80, 85 and 90% accuracy levels.

In general, the processing speed impaired group required longer SOAs to achieve identical performance to the remaining two groups (see Figure 3). On one hand, the processing speed impaired group required, on average, SOAs of 176.22 (SEM = 30.28), 204.78 (SEM = 35.42) and 238.2 ms (SEM = 41.52) to achieve 80, 85 and 90% accuracy thresholds, respectively. On the other hand, the processing speed unimpaired group required only 93.72ms (SEM = 14.52; t (11.49) = 2.46, p = 0.03), 107.44ms (SEM = 15.93; t (11.11) = 2.51, p < 0.03) and 123.51ms (SEM = 17.61; t (10.79) = -2.54, p < 0.03) to achieve identical thresholds. Similarly, the HC group achieved the 80 (M = 82.37, SEM = 8.77; t (9.33) = 2.98, p < 0.02), 85 (M = 93.65, SEM = 10.27; t (9.34) = 3.013, p < 0.02) and 90% (M = 106.85, SEM =

12.17; t (9.37) = 3.04, p < 0.02) thresholds at significantly faster SOAs than the processing speed impaired group. No significant differences between the processing speed unimpaired and HC group for the 80 (t (16) = 0.67, n.s.), 85 (t (16) = 0.73, n.s.), and 90% (t (16) = 0.78, n.s.) thresholds were observed.

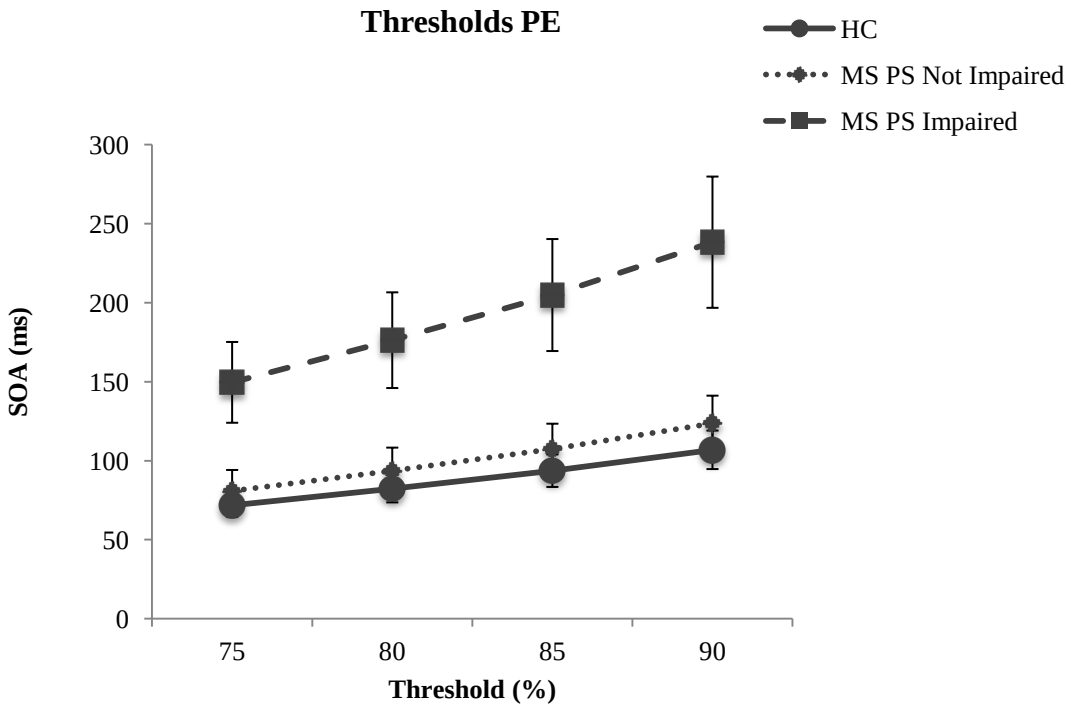

Figure 3 Thresholds for Prior-entry - For each group, SOA (in ms) was plotted as a function of Threshold (accuracy in %). Full Line- Healthy control group; Dotted line – PS not impaired group; and Dashed line – PS impaired group.

Controlling the effects of fatigue

An ANOVA was performed to test whether fatigue potentially interferes with performance. A significant main effect of the experimental block was observed (F (1,24) = 4.18, p < 0.05, η_p^2 = 0.15), although the interaction between block and group was not significant (F (2,24) = 0.89, n.s., η_p^2 = 0.07). Pairwise comparisons (adjusted for multiple comparisons with Bonferroni)

showed that no significant differences were observed within the blocks for the three groups (See Figure 4). The results suggest that there was no negative effect of fatigue influencing the performances of the three groups during the task.

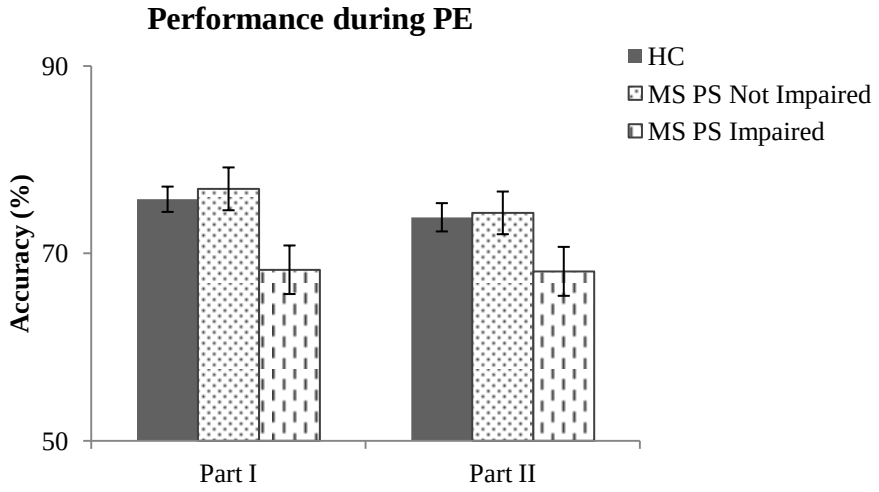

Figure 4 Performance during Prior-entry - Total correct responses by task part were plotted for each group. Gray bar – healthy control; Dotted bar – MS processing speed not impaired group; and dashed bar – MS processing speed impaired group.

Discussion

MS participants with processing speed deficits performed worse in the temporal order judgments task for shorter stimulus intervals compared to healthy controls and the MS group without processing speed deficits. MS participants with processing speed deficits required longer SOAs to achieve comparable accuracy levels when compared to the other groups. Differences were also observed for the slope of the psychometric curve. The HC and MS processing speed unimpaired group presented steeper slopes when compared to the MS

processing speed impaired group, suggesting that they required smaller steps of SOA to achieve higher accuracy levels than the MS participants with processing speed deficits. These results might be an expression of latent compromises on the ability to detect and temporally process visual information.

Experiment B: Metacontrast masking

Objectives

In Experiment B, we will use metacontrast masking, as proposed by Vorberg et al. (2003), to analyze how putative processing speed deficits in MS might be related to abnormal target detection capability, as a function of the time between the onset of the target and mask. We hypothesized that MS participants with processing speed deficits will require longer intervals between the target and mask than the remaining two groups to obtain identical levels of accuracy.

Apparatus and procedures

In this paradigm, we diminished the visibility of a briefly flashed stimulus (the target) by presenting a spatially flanking stimulus shortly after (the mask). The interaction between the characteristics of the stimuli, temporal dynamics of presentation, and conscious perception are well known (Vorberg et al., 2003). In this experiment, the targets were arrows that pointed to either to the left or to the right, and the masks were rectangles that encompassed the targets but had no orientation (i.e., only a rectangle; See Figure 5). Participants had to respond to the orientation of the target. The time between the onset of the target and mask was manipulated with durations ranging from 10 to 300 ms.

Before the experiment, participants went through a staircase procedure to define the 6 SOAs between the target and mask. The initial values of the six SOAs (10-300 ms) were modified during the staircase to elicit particular levels of accuracy (approximately 50, 55, 65, 80 and 90 to 95%). Both the experiment proper and the staircase followed the same general procedure. In every trial, the participants initially viewed a fixation cross for 600 ms that was followed by a target stimulus presented for 10 ms (See Figure 5). The location of the target was jittered so that the participants were never completely certain where the target/mask sequence would be presented. A fixation-cross then reappeared with a variable presentation duration followed by the mask presentation. To prevent indirect priming from the mask to the recognition of the target, a delay of 360ms was applied between the mask and response. The experiment consisted of three blocks, each composed by sixty-four trials. Each SOA was repeated thirty-two times. Breaks were provided between the blocks to overcome fatigue during the experiment. As in Experiment A, the participants were instructed to guess when uncertain, while providing the fastest and most accurate responses possible.

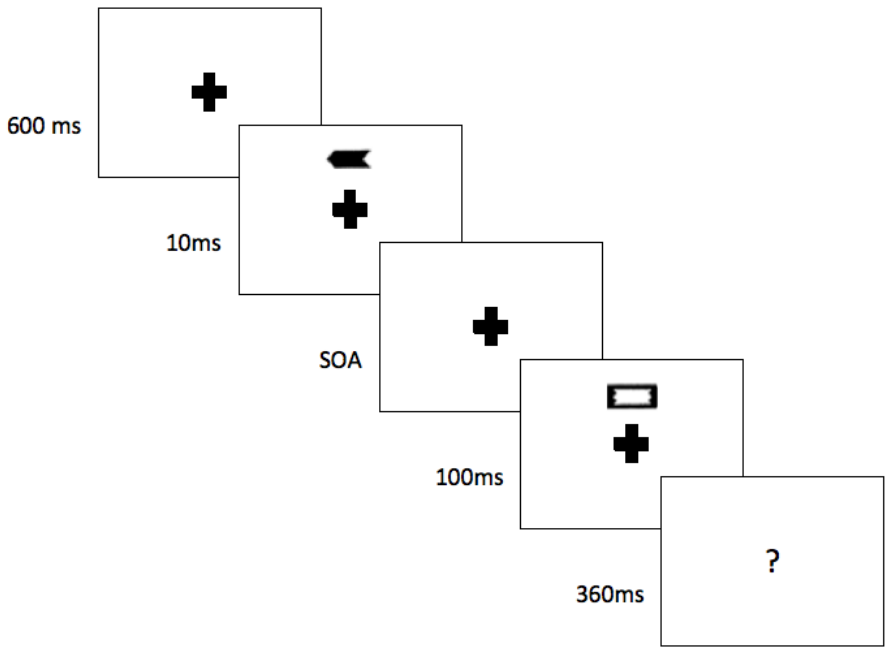

Figure 5 Metacontrast masking procedure - all runs started with a 60 ms base-line fixation period, followed by the target, presented for 10 ms. A fixation-cross was presented with variable presentation durations. Afterwards, the mask was presented for 100 ms. Between mask and response a delay of 360 ms was applied. Each run finished with the participants reporting the target direction (left or right).

Results

Four participants (three from the processing speed impaired and one from the unimpaired MS groups) were excluded from the analyses because their accuracy levels never reached values higher than 65% even on the longest SOA. The data were analyzed as in Experiment A.

75% threshold analysis

Planned contrast analyses revealed no significant differences between the processing speed impaired (M = 142.35, SEM = 36.9) and unimpaired MS groups (M = 123.43, SEM = 25.26; t (13) = 0.43, n.s.). Additionally, the processing speed impaired group typically required significant higher temporal intervals between the target and mask compared to the HC group to achieve an accuracy of 75% (M= 47.89, SEM = 11.72; t (14) = 2.71, p = 0.02). Furthermore, the processing speed unimpaired MS group also differed significantly from the HC (t (9.94) = 2.71, p = 0.02). The MS groups required significantly longer SOAs, when compared to the HC group, to achieve good overall performance, but did not differ significantly from one another (See Figure 6).

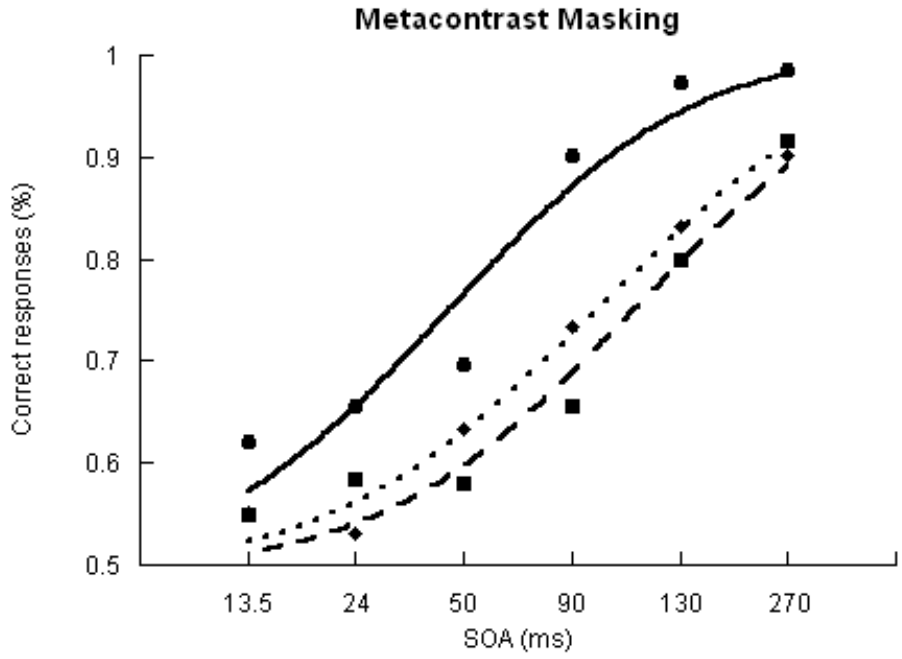

Figure 6 Metacontrast masking - In this figure, we plotted percent correct performance as a function of SOA. Actual data from the impaired group, non-impaired group and HC group are presented as a filled square (■), a filled diamond (●), and a filled circle (◆), respectively. Lines correspond to fitted data using the probit function. Full Line corresponds to fitted data from the Healthy control group. The Dotted line corresponds to fitted data from the MS processing speed not impaired group. The Dashed line corresponds to fitted data from the MS processing speed impaired group.

Slope of the fitted psychometric curve

No significant differences were observed between the slopes of the psychometric curve (probit function) for the processing speed impaired (M = 0.021, SEM = 0.011) and unimpaired groups (M = 0.014, SEM = 0.003; t (13) = 0.635, n.s.), even when compared to the HC group (M = 0.021, SEM = 0.005; t (14) = - 0.003, n.s.). Similarly, no significant difference was observed between the slopes of the processing speed unimpaired and HC groups (t (15) = -1.228, n.s.).

In general, the psychophysical curve demonstrated a good fit to the data (MS processing speed impaired group r = 0.93; SEM = 0.1; 0.86-0.96; MS processing speed unimpaired group r = 0.91; SEM = 0.01; 0.85-0.96; and HC r = 0.93; SEM = 0.03; 0.68-1.00).

The 80, 85 and 90% thresholds

We analyzed the differences between the groups for other thresholds (80, 85 and 90%) (See Figure 7). Similar to what was observed for the 75% threshold, the MS groups did not differ between one another for 80, 85 and 90% thresholds. On one hand, the processing speed impaired group typically required 163.65ms (SEM = 41.23), 186.45ms (SEM = 46.23) and 213.13ms (SEM = 52.40), to accomplished 80, 85 and 90% of correct responses, respectively, whereas the processing speed unimpaired group required 143.23ms (SEM = 28.89; t (13) = 0.41, n.s.), 164.41ms (SEM = 32.98; t (13) = 0.4, n.s.), and 189.21ms (SEM = 37.95; t (13) = 0.38, n.s.). On the other hand, significant differences were observed between each MS and the HC groups. Both MS groups required longer SOAs to achieve the same level of accuracy as the HC group. More specifically, healthy controls required SOAs of 59.78 (SEM = 10.67), 72.5 (SEM = 10.03), and 87.38 ms (SEM = 10.04) to achieve 80, 85 and 90% thresholds, which were significantly faster compared to the processing speed impaired [80% (t (14) = 2.73, $p < 0.02$); 85% (t (14) = 2.72, $p < 0.02$) and 90% (t (6.44) = 2.36, $p = 0.05$)], and unimpaired groups [80% (t (8.89) = 2.71, $p = 0.24$); 85% (t (8.29) = 2.67, $p < 0.3$) and 90% (t (7.98) = 2.59, $p = 0.03$)].

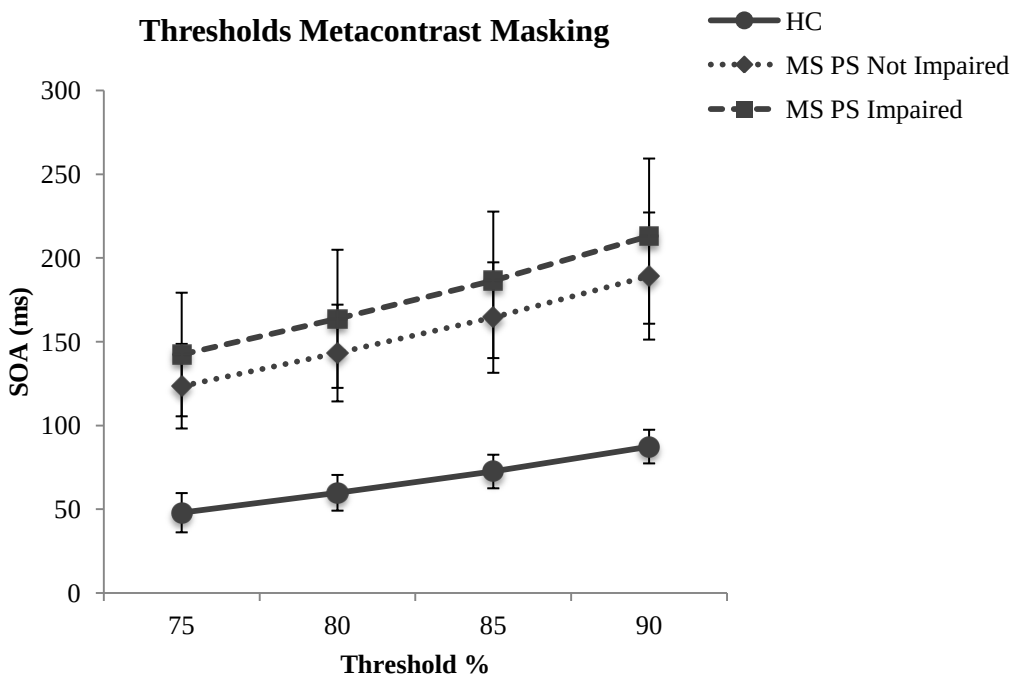

Figure 7 Thresholds for Metacontrast masking - For each group, SOA (in ms) was plotted as a function of Threshold (accuracy in %). Full Line- Healthy control group; Dotted line – PS not impaired group; and Dashed line – PS impaired group.

Controlling the effects of fatigue

An ANOVA demonstrated no significant effect for either the blocks ($F(1,20) = 3.32$, n.s., $\eta_p^2 = 0.14$) or group and block interaction ($F(2,20) = 1.3$, n.s., $\eta_p^2 = 0.12$). Therefore, it is possible to conclude that fatigue did not negatively interfere with performance during the experiment for the three groups, which is in accordance with Experiment A and can be shown in Figure 8.

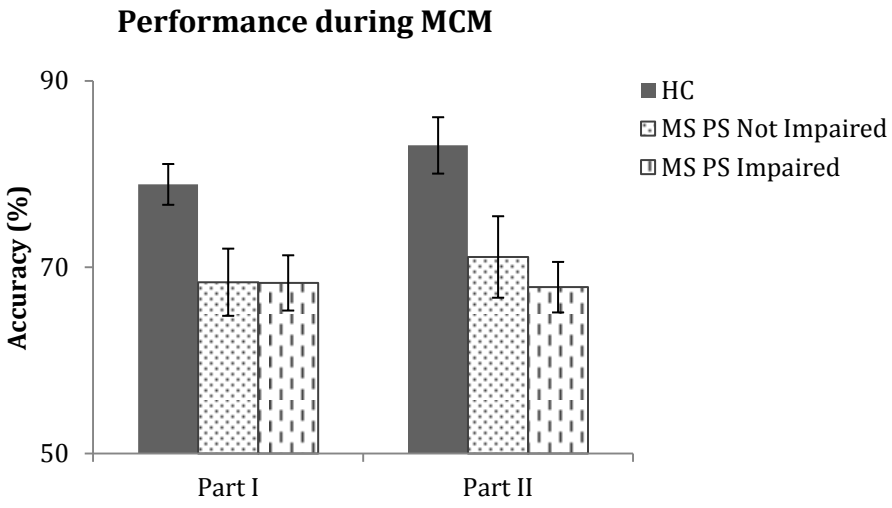

Figure 8 Performance during metacontrast masking – Total correct responses by task part were plotted for each group. Gray bar – healthy control; Dotted bar – MS processing speed not impaired group; and dashed bar – MS processing speed impaired group.

Discussion

Both MS groups present a significant delay in visual processing compared to healthy controls. Longer SOAs between the target and mask are necessary for MS participants to achieve the same level of accuracy as healthy controls. The results do not support what was predicted because both MS groups significantly differ from healthy control group. It is notable that no differences were observed between the groups regarding the psychophysical curve slope. It is then possible to conclude that both MS participants executed the tasks similarly to healthy controls; however, a shift toward longer SOAs was observed.

Experiment C: Rapid serial visual presentation

Objectives

In this experiment, we implemented an RSVP task, similar to what was proposed by McKeeff et al. (2007). We hypothesized that MS participants with processing speed deficits would show limitations to the visual system processing capacity. In particular we expected this group to present steeper deficits in the ability to perceive as a function of the presentation rates when compared to the remaining two groups.

Apparatus and procedures

A rapid serial visual presentation paradigm was adapted from McKeeff et al. (2007). In each experimental run, participants viewed stimulus sequences of faces and houses presented at varying temporal rates of 2.6, 4.8, 6.4, 9.6 and 19 items/second (monitor frame rate 75 Hz). No blank period or visual mask occurred between the successive images.

Each run began with a 16-s fixation-baseline period. Two target images (a face and house) were then presented for 5000 ms followed by the presentation of the sequence of visual stimuli (8 s), and a free time period to provide a response (See Figure 9). The duration of an entire run was 256 s. The stimulus block consisted of a randomly generated sequence of distractor images, selected from the same semantic category as the targets (houses and faces). The target image was introduced at a random position within the sequence provided that it was not presented on the first or the last positions. The order of the presentation rate and target identity were counterbalanced across runs. Each participant performed a total of one hundred and fifty experimental runs, seventy-five faces and seventy-five houses, for a total

of three stimulus blocks for each combination of stimulus type and temporal rate. At the end of each block, the participants were asked to report which of the two target images appeared in the sequence by pressing one of two keys on the computer keyboard.

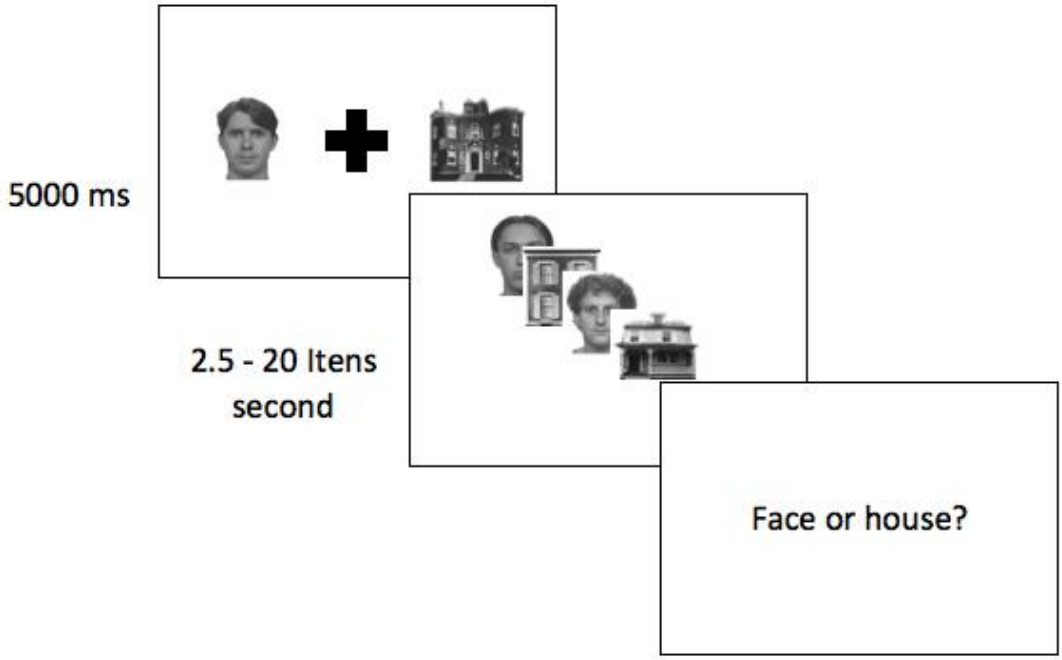

Figure 9 Rapid serial visual presentation procedure - Each run started with a fixation-baseline period, followed by 5000ms of the two-target image presentation. Stimulus block consisted of a randomly generated distracter image sequence, presented with variable temporal rates. Each run ends with an open time for participants report which target image appeared on the stimulus sequence.

Results

In total, five participants (one healthy control, three from the MS processing speed impaired group and one from the MS processing speed unimpaired group) were excluded from the analyses because they did not achieve levels of accuracy above 65% even for the longest SOA. The data were analyzed as in Experiment A.

Significant main effects were observed for SOA (F (2.74, 51.96) = 43.65, p < 0.001, η_p^2 = 0.7) and group (F (2,19) = 3.84, p < 0.05, η_p^2 = 0.29) but not stimuli (F (1,19) = 0.58, n.s., η_p^2 = 0.03) or group, SOA and stimuli interaction (F (8,76) = 1.31, n.s., η_p^2 = 0.12). It was concluded that the overall performance was influenced by SOA and group but not the stimulus nature. Because recognition was not affected by the stimulus nature, we collapsed the trails from each category.

75% threshold analyses

Planned contrast analyses demonstrated that the processing speed impaired group (M = 304.99 ms/image, SEM = 45.43) required significantly slower temporal rates to achieve a 75% correct performance when compared to the unimpaired (M = 140.40 ms/image, SEM = 45.95; t (12) = 2.49, p < 0.03) and HC groups (M = 156.05 ms/image, SEM = 35.51; t (12) = 2.62, p = 0.02). Furthermore, the processing speed unimpaired and HC groups did not differ in the temporal rate required to achieve a 75% threshold (t (14) = -0.27, n.s.; See Figure 10).

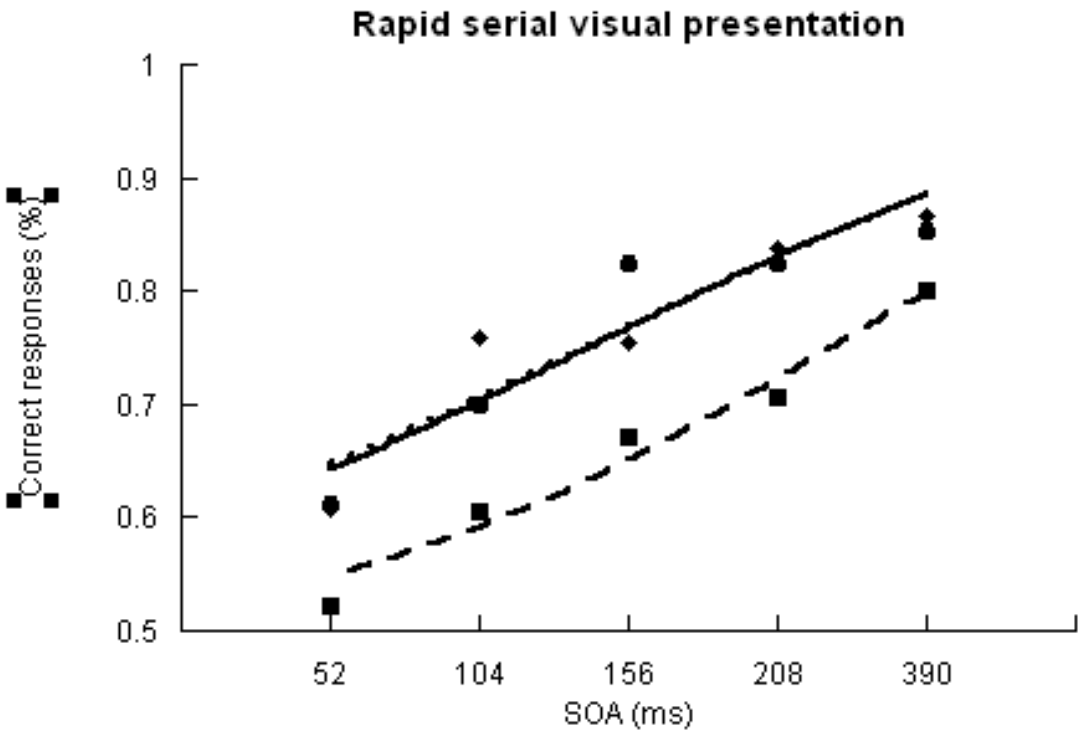

Figure 10 Rapid serial visual presentation - In this figure, we plotted percent correct performance as a function of SOA. Actual data from the impaired group, non-impaired group and HC group are presented as a filled square (■), a filled diamond (●), and a filled circle (◆), respectively. Lines correspond to fitted data using the probit function. Full Line corresponds to fitted data from the Healthy control group. The Dotted line corresponds to fitted data from the MS processing speed not impaired group. The Dashed line corresponds to fitted data from the MS processing speed impaired group.

Slope of the fitted psychometric curve

Regarding the psychophysics curve slope, no differences were observed between the MS groups (for the processing speed impaired group M = 0.004, SEM = 0.001; for the MS processing speed unimpaired group M = 0.004, SEM = 0.001; t (12) = - 0.03, n.s.). No differences were observed regarding the slope of the psychometric curve between the MS and HC groups (M = 0.004 ms/image, SEM = 0.001), MS processing speed impaired and HC groups (t (12) = -0.05, n.s.); and MS processing speed unimpaired and HC groups (t (14) = - 0.03, n.s.). Typically, the psychophysical curve demonstrated a satisfactory fit to the data (MS processing speed impaired group r = 0.89; SEM = 0.2; 0.81 – 0.94; MS processing speed unimpaired group r = 0.78; SEM = 0.05; 0.44 – 0.92; and HC r = 0.79; SEM = 0.05; 0.55 – 0.93).

The 80, 85 and 90% thresholds

A difference was observed between the processing speed impaired (M = 360.5 ms/image, SEM = 51.62) and unimpaired groups (M = 214.56 ms/image, SEM = 44.24) at the 80% threshold (t (12) = 2.15, p = 0.05). However, no differences were observed between these two groups at the 85% (processing speed impaired M = 419.88 ms/image, SEM= 59.58; and unimpaired groups M = 293.92 ms/image, SEM = 51.73; t (12) = 1.6, n.s.) or 90% thresholds

(processing speed impaired M = 489.38 ms/image, SEM = 70.02; and unimpaired groups M = 386.78 ms/image, SEM = 68.39; t (12) = 1.03, n.s.). Similarly, the processing speed impaired group differed compared to the HC group at the 80% threshold (M = 215.36 ms/image, SEM = 39.26; t (12) = 2.28, p = 0.04) but not at the 85% (M = 278.82 ms/image, SEM = 45.88; t (12) = 1.9, n.s.) or 90% thresholds (M = 353.20 ms/image, SEM = 55.81; t (12) = 1.5, n.s.). No significant differences were observed between the processing speed unimpaired and HC groups at the 80% (t (14) = -0.1, n.s.), 85% (t (14) = 0.22, n.s.), or 90% thresholds (t (14) = 0.38, n.s.; see Figure 11).

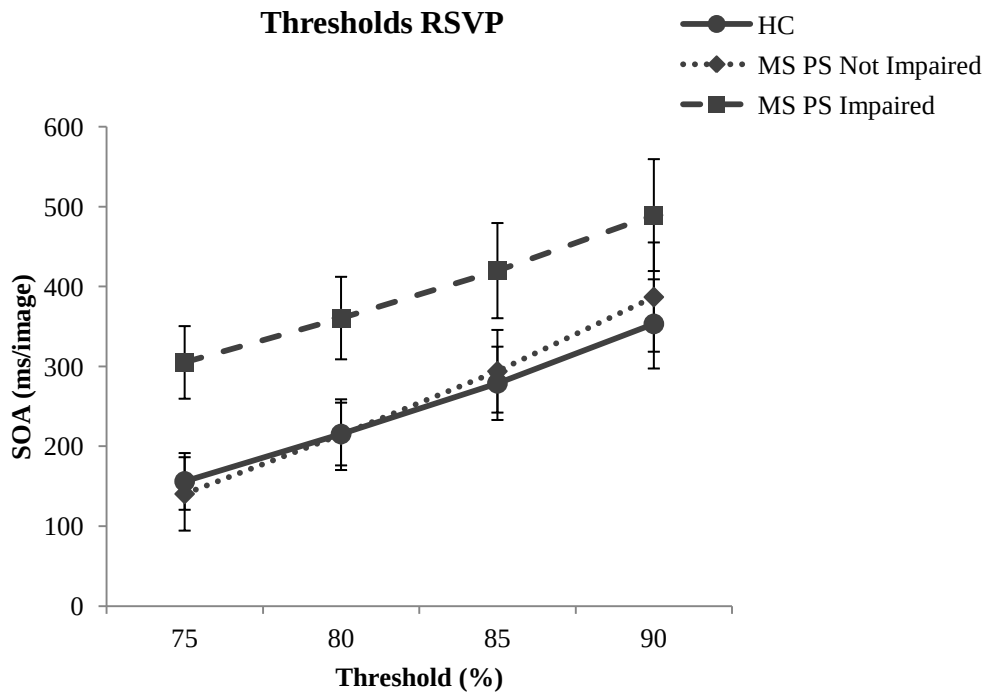

Figure 11 Thresholds for rapid serial visual presentation - For each group, SOA (in ms) was plotted as a function of Threshold (accuracy in %). Full Line- Healthy control group; Dotted line – PS not impaired group; and Dashed line – PS impaired group.

Controlling the effects of fatigue

No significant main effect was observed for task block (F (2,38) = 3.01, n.s., η_p^2 = 0.14) or group and task interaction (F (4,38) = 1.03, n.s., η_p^2 = 0.1). Similar to the previous two experiments, the performances for the three groups did not appear to be affected by possible cognitive fatigue resulting from the experiment (See Figure 12).

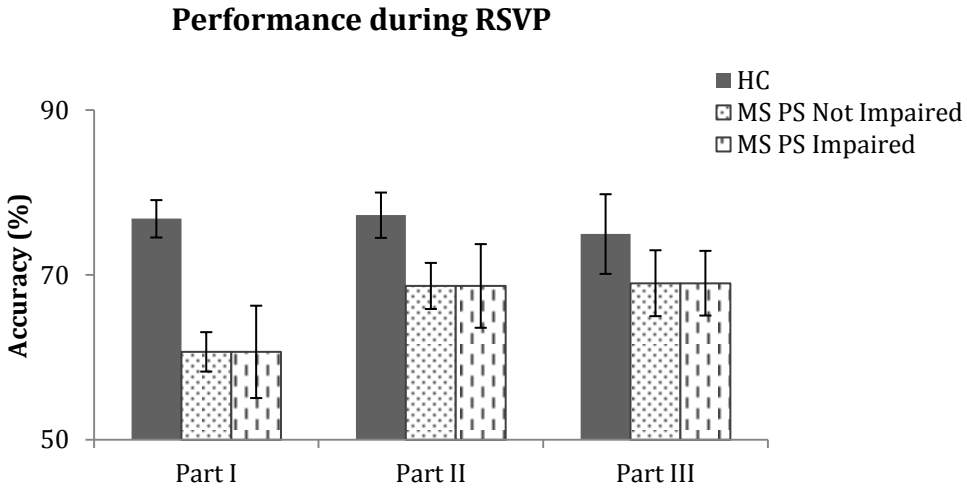

Figure 12 Performance during rapid serial visual presentation - Performances for each group, by the three task blocks. Blue bar – HC percent correct responses for each block; Green bar – Processing Speed not impaired group; and Red bar – Processing Speed impaired group.

Discussion

As previously demonstrated (McKeeff et al., 2007) accuracy levels decreased as a function of the presentation rate - the faster the presentation, the worse the result. In accordance with the literature (McMains & Somers, 2004; Potter, 1975), it is expected that recognition performances begin to decline at presentation rates of 125-100 ms/image. In the present

study, the recognition performance for both healthy control and processing speed unimpaired groups typically began to decline at 156.05 and 140.40 ms/image, similar to the results of McKeeff and colleagues (2007). In contrast, accuracy levels for the processing speed impaired group were compromised even at slower presentation rates (304.99 ms/image), which is significantly different from what was obtained for the two remaining groups. This suggests that processing speed deficits are associated with a higher limitation in the temporal processing capacity of the visual system.

Differences in the temporal rates between the processing speed impaired and remaining two groups extend for an intermediate performance level of 80% accuracy, but not for performances equal to or above 85% correct performance. It appears that the processing speed impaired group shows an abnormal limitation on the capacity to process visual information at fast presentation rates; however, this limitation tends to cease for slow presentation rates. The problem appears to be related with a temporal limitation of the visual system, rather than with an impaired capacity to perform a recognition task or process visual information.

General discussion

The present study suggests that processing speed deficits in multiple sclerosis might be related to a sensorial temporal limitation of the visual system. Processing speed deficits were associated with a decreased capability to detect visual stimuli and higher limitation in temporal processing capacity. Moreover, the temporal dynamics of visual processing appear to be compromised for participants with multiple sclerosis, independent from cognitive performance.

A significant decrease in the sensitivity to detect and process temporally visual information by MS participants with processing speed deficits was observed using the prior-entry procedure. MS participants with processing speed deficits demonstrated a significant different task performance compared to the remaining two groups, as demonstrated by the psychophysical curve slope.

In accordance with these results, the neuropsychological tasks measuring simple reaction times (Reicker, Tombaugh, Walker, & Freedman, 2007) and attention processes (Kavcic & Scheid, 2011) in multiple sclerosis samples had previously revealed that processing speed deficits are related to abnormalities in the capacity to detect visual information. The present study provides further evidence by showing that such abnormalities could be a result of a low-level visual processing deficit. The tasks had, as a major strength, the capacity to provide a direct index of the potential delays generated without the regular confounds resulting from the more motoric processes involved in masking a speeded response.

The temporal dynamics of visual processing were observed to be abnormal for both groups of participants with multiple sclerosis. According to the present results, participants with multiple sclerosis, independent from cognitive performance, typically show an abnormal sensitivity to masking effects; longer periods between the target and mask were required to overlap the negative influence of the mask on target processing.

Low-level theories postulated that mask effects occur because the mask interrupts the ongoing early visual processing of the target, thus inhibiting the target from entering conscious processing (Breitmeyer & Ogmen, 2000). Recent theories argue that high-level processing also have an important role and interact with masking (Boyer & Ro, 2007; Enns & Di Lollo, 2000).

In a study with relapse-remitting multiple sclerosis participants in early stages of the disease, Reuter et al. (2007), used a backward masking paradigm, and demonstrated that subliminal priming is preserved, indicating normal non-conscious processing. However, MS participants required significantly higher threshold to access consciousness. The authors then concluded that the results might be an expression of the diffuse white matter damage that is frequently observed at early stages of multiple sclerosis, which affects the cortical recurrent activity essential to access consciousness (Reuter et al., 2007). These results could also be associated with an early visual dysfunction, at the level of the optic nerve or early visual pathways, which conduct information to the primary and secondary visual areas. However, the authors rejected these alternative explanations based on the sample characteristics.

The neural causes of our metacontrast results may well be related with white matter integrity, as proposed by Reuter et al., (2007, 2009). However, because twelve of our participants with multiple sclerosis reported a history of acute episodes of neuro-ophthalmic syndromes, we cannot exclude that the results could be an expression of latent early visual dysfunction at the level of the optic nerve or early visual pathways.

For the MS group with processing speed deficits, the problem does not seem to be an impaired capacity to perform recognition tasks or process visual information, but rather a higher limitation in the temporal processing capacity of the visual system.

In a fMRI study using a RSVP task, McKeeff et al. (2007) demonstrated an association between the rapid presentation rates and peak activities in areas V1-V3, whereas intermediate rates were linked to an activity increase in area V4, and areas FFA and PPA showed higher activations for the slowest presentation rates. The authors postulated that as visual information is transferred from early to higher areas of visual processing, a progressive decrease in

sensitivity to high temporal rates might occur and lead to a continuing shift in peak sensitivity toward lower temporal rates.

Considering our results, the significant higher limitation in the temporal processing capacity of the visual system observed behaviorally for participants with processing speed deficits, could be related with two possible neural causes. On one hand, our results might be related to a decreased in sensitivity at higher levels of visual processing, namely areas PPA and FFA, revealing a steeper decline in the sensitivity to high temporal rates as information is transferred from early to higher areas of visual processing. But we cannot exclude that the decrement in performance is related with an abnormal activation of early visual areas V1-V3, or that different neural functioning abnormalities within low- and high-level visual system areas.

All of participants with MS in the processing speed impaired group reported a history of neuro-ophthalmic syndrome during the course of the disease, whereas only 33.33% from the without impaired processing speed group did so. According with the literature (Burton et al., 2011; Frohman et al., 2005; Frohman et al., 2010; Maxner, 2006), a history of neuro-ophthalmic syndromes is associated with long-term anatomical and functional abnormalities, even when clinical recovery is achieved. We hypothesized that these deficits might be related to the abnormal sensitivity of the visual system to temporally process information, and such deficits could be related to the processing speed deficits that are often observed in MS samples.

Supporting this hypothesis, Toledo et al. (2008) demonstrated that poor performance on the SDMT, an often-used visual-based task to measure processing speed, were associated with decreases of the RNFL in multiple sclerosis.

More studies are required to understand the neural causes of the potential sensorial temporal limitation of the visual system demonstrated in the present study, in participants suffering from relapse-remitting multiple sclerosis with processing speed deficits. We hypothesize that the results observed in the present study might be related to two potential neuronal causes. Because of latent abnormalities within the visual system, multiple sclerosis participants with processing speed deficits might show a decrease or absence of sensitivity to process fast visual information, thus expressing a low-level sensorial deficit. However, these results might also be related to higher levels of visual processing deficits. It is also possible that low and high levels of visual processing deficits interact and significantly contribute to the putative processing speed deficits that are often associated with multiple sclerosis.

GENERAL CONCLUSIONS

During the course of the first chapters of this dissertation, we explored the clinical features of Multiple Sclerosis. Understanding MS and its concomitant disabilities is of major importance, not only because it significantly compromises patients and their families' overall quality of life, but also due to the astronomical negative impact of the disease on society. With a relatively early age of onset, MS compromises productivity, social interactions, and represents high direct and indirect healthcare costs.

Although the visual system function is largely accepted to be vulnerable to disease, implications for cognitive function are not completely understood. Visual system abnormalities have been often associated with a history of neuro-ophthalmic syndromes (though they can even appear in their absence). Cognitive deficits, and, in particular processing speed deficits, are also often associated with MS. Similar to neuro-ophthalmic syndromes, cognitive deficits might appear at onset or during the course of the disease. Two studies were developed with the aim to further understand visual processing speed deficits in relapse-remitting MS (RRMS).

The first study presented was designed to explore if a history of a neuro-ophthalmic syndrome would be related with poorer performances in visual processing speed deficits, measured through well known neuropsychological tests. Three groups were composed: two groups of participants with RRMS (one with participants reporting a history of a neuro-ophthalmic syndrome, the other composed of participants without a history of a neuro-ophthalmic syndrome) and a control group of participants without any history of a neurological disease. Results suggest that a history of neuro-ophthalmic syndromes is related with the poorest performances in vision-based processing speed tasks, albeit with preserved ability to process visual information.

We then hypothesized that visual system abnormalities, associated with neuro-ophthalmic syndromes, might be related with a limitation of the visual system to process visual information with an regular speed. If on the one hand, after neuro-ophthalmic syndromes, clinical recovery is often reached, thus leading to preserved ability to perform visual tasks, on the other hand, long-term abnormalities do in fact remain, probably resulting in a temporal limitation of the visual system, that is visual information is processed with a significant delay.

To further understand how the putative abnormal temporal properties of visual processing might be related with processing speed deficits in MS, we developed study two. The MS sample was divided into two groups, the group with processing speed deficits and the group without processing speed deficits, taking into consideration performance on the SDMT. To understand MS participants' performances, a group of healthy volunteers was added as a control group. Processing speed deficits were associated with a decreased capability to detect fast presentations of visual stimuli, as well with a higher limitation in the temporal processing capacity. Moreover, the temporal dynamics of visual processing seems to be compromised, on average, for participants with multiple sclerosis, regardless of cognitive performance.

Based on the assumption that visual system integrity is vulnerable to MS pathological features, we suggest that processing speed deficits in MS might be associated with a reduction in the visual system's temporal sensitivity. More studies are needed to understand the neural causes of the potential sensorial limitation of the visual system; nevertheless, two possible neural causes might be discussed. Due to latent abnormalities within the visual system, multiple sclerosis participants with processing speed deficits might show a decrease or even an absent sensitivity to process fast visual information, expressing a low-level sensorial deficit. Yet, these behavioral results might also be related with more high-levels of visual processing deficits,

rather more associated with deficits in the capability to process visual information. It is also possible that low- and high-levels of visual processing deficits interact, contributing significantly to the putative processing speed deficits so often associated with multiple sclerosis.

Important insights concerning MS pathophysiology, disease progression and severity, as well neurodegeneration, might easily be assessed from an analysis of the different components of the visual system, some authors have claimed (Burton et al., 2011; Frohman et al., 2008a; Frohman et al., 2008b; Siger et al., 2008; Trip et al., 2006). Our results further support the importance of studying the visual system, proposing that the visual system might provide further insights into visual processing speed deficits frequently associated with MS. The potential relation between the visual system and cognitive function was already proposed in the past (Bruce et al., 2007; Davis et al., 2009; Feaster & Bruce, 2011; Fielding et al., 2009a, 2009b). However, and as far as we know, those were the first studies relating processing speed deficits with a history of neuro-ophthalmic syndromes and, as well, with abnormal temporal dynamics of processing.

Overall, it seems that participants with a history of neuro-ophthalmic syndromes, with associated potential visual system limitations, are able to accurately process visual information, but with a significant delay. Furthermore, visual processing speed deficits were associated with a limitation in the temporal processing capacity of the visual system. Further studies are needed to understand the neural causes of our results.

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ANNEXES

ANNEX 1: CONSENT TO PARTICIPATE IN A RESEARCH STUDY

KESSLER FOUNDATION RESEARCH CENTER
INSTITUTIONAL REVIEW BOARD

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE OF STUDY: Visual Processing Speed in Multiple Sclerosis

RESEARCH STUDY #: E-700-11

I, _____, have been asked to participate in a research study under the direction of Dr. Chiaravalloti. Other professional persons who work with her as study staff may assist or act for her. All research projects carried out at Kessler Foundation Research Center are covered by the rules of both the Federal Government and Kessler Foundation Research Center.

The Information provided may contain words I do not understand. I will ask the study doctor or the research staff to explain any words or procedures that I do not understand.

PURPOSE:

The purpose of this study is exploring the relationship between visual speed of processing and cognitive deficits in individuals with Multiple Sclerosis. It is our aims evaluate patterns of visual processing and how they are related with demographic and clinical measures, as well cognitive function.

DURATION:

My participation in this study will last for either a half hour, or if I qualify for the entire study, about 4 hours, divided into two evaluation sessions for 2 hours each.

PROCEDURES:

I have been told that, during the course of this study, the following will occur:
First, I will undergo neuropsychological testing at Kessler Foundation Research Center. This will be a brief evaluation, lasting only 30 minutes, which will determine if I meet study criteria. If I do not meet study criteria, this will end my participation in the study and I will receive $20 for my time.
If I do meet study criteria, I will be enrolled in the study and my participation will proceed as follows.

The rest of my participation in this study will last for about 31/2 hours, divided into two evaluation sessions.
During day one I will review my medications with the investigator and complete a questionnaire that asks

(For use by IRB Administrator)
IRB APPROVAL EXPIRES
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Participant's Initials: _____

about my mood. On both days, I will complete some paper and pencil test examining my speed of processing, my capacity for learning new information, and pay attention for long periods of time, etc. I will also undergo visual processing speed exercises in a computer.

If I have participated in other IRB approved studies at Kessler Foundation Research Center, test results from the previous study may be used for this protocol, and it is possible that some of these tests will not need to be re-administered.

PARTICIPANTS:

I will be one of about thirty (40) participants in this study; 25 subjects with multiple sclerosis and 15 healthy volunteers.

INCLUSION CRITERIA:

To be eligible to entry into this study, I must meet **all** the following criteria before study enrollment:

I am between 25 and 55 years old.
According to my medical records, I have a history of Multiple Sclerosis (only for participants with multiple sclerosis).
I am physically able to see the testing materials and complete the tests.

EXCLUSIONS:

If any of the statements below apply to me, I need only tell the researcher that one or more of the statements pertain to me. To ensure my privacy and confidentiality, I need not reveal which of the statements apply to me. If I choose to tell the investigator which of the statements apply to me, the information will be kept strictly confidential.

I will inform the researcher if any of the following statements apply to me:

I have a history of treated or untreated severe mental (bipolar disorder, schizophrenia)
I have a history of traumatic brain injury, stroke, or other neurologic illness
I have had a clinically significant relapse within the past 4 weeks.
I have a history of drug or alcohol abuse
I am taking certain medications, such as: steroids, benzodiazepines, and/or neuroleptics.

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RISKS/DISCOMFORTS:

I have been told that the study described above may involve the following risks and/or discomforts:

Participant's Initials: _____

The study involves minimal potentials risks. Risks from undergoing neuropsychological or visual processing speed paradigms are mild fatigue or mild frustration. If this happens, I will tell the examiner and request a break. There also may be risks and discomforts that cannot be foreseen.

BENEFITS:

I have been told that I will receive no direct benefit from my participation in this study, but the information obtained from this investigation may help the researchers to better understand visual processing speed and the relationship with cognitive function in Multiple Sclerosis.

ALTERNATIVES:

The only alternative is to choose not to participate in this study.

NEW FINDINGS:

During the course of the study, I will be told about any new findings that might affect my willingness to remain in the study.

CONFIDENTIALITY:

Every effort will be made to maintain the confidentiality of my study records.
Officials of Kessler Foundation Research Center, and the sponsoring company – Fundação para a Ciência e Tecnologia (Portuguese Foundation for Science and Tecnhology), will be allowed to inspect sections of my medical and research records related to this study. If the findings from the study are published, I will not be identified by name. My identity will remain confidential unless disclosure is required by law.

FINANCIAL COSTS TO THE PARTICIPANTS:

I understand there will be no cost to me for my participation in this study.

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PAYMENT FOR PARTICIPATION:

I have been told that I will receive $20 if I only participate in the screen, or $100 for my participation in the study according to the following schedule: a check will be mailed to my home within 2 weeks after the last testing session.

Participant's Initials: _____

MEDICAL THERAPY FOR INJURY:

Medical therapy will be arranged for me by the Principal Investigator for any physical injuries sustained as a direct consequence of my participation in this research. My health insurance carrier, managed care provider or other third party payer will be billed for the cost of this medical therapy. All claims for unreimbursed expenditures for medical therapy should be made to the Principal Investigator. I understand that there will be no cost to me for the therapy. However, no other financial compensation is offered to me in the event of physical injuries sustained as a direct consequence of my participation in this research.

RIGHT TO REFUSE OR WITHDRAW:

I understand that my participation is voluntary and I may refuse to participate, or may discontinue my participation at any time, without penalty or loss of benefits to which I am otherwise entitled. I also understand that the investigator has the right to withdraw me from the study at any time.

INDIVIDUAL(S) TO CONTACT:

If I have any questions about my treatment or the research procedures, I can contact:

Dr. Nancy Chiaravalloti, PhD, Director of the Neuropsychology and Neuroscience Laboratory at 973-324-8440

If I have concerns only regarding my **rights as a research participant**, I may contact the Malica Dock, IRB Coordinator, at 1-800-648-0296, extension 6972.

I will receive a copy of this consent form if I agree to participate in this research study.

_____ Participant's Initials

(For use by IRB Administrator)

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Participant's Initials: _____

SIGNATURE OF PARTICIPANT

I have read this entire form, or it has been read to me, and I understand it completely. All of my questions regarding this form or this study have been answered to my complete satisfaction. I agree to participate in this research study.

Participant Name:_____Signature:_____

Date:_____

SIGNATURE OF INVESTIGATOR OR RESPONSIBLE INDIVIDUAL

To the best of my knowledge, the participant, _____, (or his /her parent/legal guardian) has understood the entire content of the above consent form, and comprehends the study and its risks as well. The participant's questions and those of his/her parent/legal guardian have been accurately answered to his/her/their complete satisfaction.

Investigator Name:_____Signature:_____

Date:_____

SIGNATURE OF WITNESS

I further attest that I was present as a witness throughout the above mentioned oral presentation, including the answering of any and all questions raised by the participant.

Witness Name:_____Signature:_____

Date:_____

(For use by IRB Administrator)

IRB APPROVAL EXPIRES

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ANNEX 2: AUTHORIZATION TO USE AND DISCLOSE
PROTECTED HEALTH INFORMATION FOR RESEARCH PROPOSES

KESSLER FOUNDATION RESEARCH CENTER

HIPAA AUTHORIZATION
No Expiration Date
KESSLER FOUNDATION RESEARCH CTR.

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES

Sponsor: Fundançăo para a Ciência e Tecnologia (Portuguese Foundation for Science and Technology)

Investigator-Name, Address and Phone No: Nancy Chiaravalloti PhD; Kessler Foundation, 300 Executive Drive, Suite 70, West Orange, NJ 07052. Telephone number: 973-324-8440

Study Title and Number: Visual Processing Speed in Multiple Sclerosis (E-700-11)

Research, Privacy, and the new Health Insurance Portability and Accountability Act (HIPAA)

1. ***What is the purpose of this form?***

We would like to use your health information for research. This information includes data that identifies you during the process of data collection. The Federal Health Insurance Portability and Accountability Act (HIPAA) of 1996 requires us to get your approval to use health information about you that identifies individuals. This approval is called an Authorization.

By signing this Authorization form, you are giving permission for the use of your protected health information for research purposes. This information may include data that identifies you. Please carefully review the information below. If you agree that we can use your protected health information, you must sign and date this form to give your approval.

2. ***What protected health information do the researchers want to use?***

The researchers want to copy and use the portions of your medical record that will be needed for their research. If you participate in this research study, information that will be used and/or released may include the following:

We will use your information from your medical records, case report forms, both clinical and research observations made while you take part in the research. Clinical information collected will include any new diagnoses, reported symptoms, changes in body appearance, how well you feel physically and emotionally, what medications you are prescribed.

3. ***Why do the researchers want my protected health information?***

In enacting HIPAA, Congress mandated the establishment of Federal standards for the privacy of individually identifiable health information. The Privacy Rule establishes

safeguards to protect the confidentiality of medical information and provides guidelines for research organizations such as Kessler Foundation Research Center to use or disclose protected health information for purposes preparatory to research, such as to aid study recruitment. We believe that the protection of identified medical information will facilitate medical research because research participants know that their information is protected in accordance with the Privacy Rule.

4. ***Who may see your protected health information for this research study:***

Your health information may be shared with people and researchers at this institution and associates of the sponsor(s), university, clinic or hospital who help with the research. We may share this information with others who are in charge of the research, who pay for or work with us on the research or those who make sure that we do this research properly. This authorization form will explain how your protected medical information will be used and shared (disclosed) in this research study.

To meet regulations or for reasons related to this study, the study team may share a copy of this approval form and records that identify you with the following people:

- The Institutional Review Board - a committee that reviews research studies for the protection of the people who participate in research.
- Auditors from this institution (the Kessler Foundation Research Center), the sponsor or government agencies responsible for the conduct of research to make sure we are following regulations, policies, and study plans.
- Members of the study team, including Silvana Lopes Costa, MsC; Nancy Chiaravalloti,PhD; John DeLuca, PhD; Nancy Moore, M.A.; Óscar Gonçalves, PhD; Jorge Almeida, PhD
- The Finance Dept. of the Kessler Foundation, who will prepare subject payments for participation in the study
- Other organizations: School of Psychology, Minho University,Portugal

You have the right to look at your study information at the study doctor's office and to ask (in writing) for corrections of any of your information that is wrong.

We will make every effort to keep information we learn about you private. However, research involves gathering, recording, and transferring information that needs to be verified and other people may need to see the information (these others are listed on this form). Some of these people may share your health information with someone else. If they do, the same laws that the hospital, clinic or institution must obey to protect your health information may not apply to these other people or institutions.

5. ***What happens if I sign this Authorization?***

If you agree to give approval to use and share your protected information as described in this form, your authorization will not expire unless you cancel it. The information collected during your participation for this study will be kept indefinitely. By signing this approval form, you give us permission to use and share your protected health information.

6. ***What happens if I do not sign this approval form?***

If you do not sign this approval form, you will not be able to take part in the research study for which you are being considered.

7. ***If I sign this form, will I automatically be entered into the research study?***

No, you cannot be entered into any research study without further discussion and a separate consent form. After discussion, you may decide to take part in the research study. At that time, you will be asked to sign a specific research approval (Informed Consent) form.

8. ***What happens if I want to remove my approval?***

You can change your mind at any time and remove your approval to allow your protected health information to be used in the research. If this happens, you must remove your approval in writing. Beginning on the date you remove your approval, no new protected health information will be used for research. However, researchers may continue to use the health information that was provided before you withdrew your approval.

If after signing this form, you want to remove your approval, please contact the person(s) below. She will make sure your written request to remove your approval is processed correctly.

Nancy Chiaravalloti PhD
Kessler Foundation
300 Executive Drive, Suite 70
West Orange, NJ 07052
973-324-8440

9. ***How long will these approvals last****?*

If you agree by signing this form that researchers can use your protected health information, this approval has no expiration date. However, as stated above, you can change your mind and remove your approval at any time.

Questions should be directed to the research staff person who is reviewing this form with you. You can also call the Kessler Foundation Research Center Privacy Board – *John DeLuca, Ph.D., ABPP at (973) 324-3572*

SIGNATURE PAGE

This form does not replace the Informed Consent to participate in research. It provides additional information related to the use and disclosure of your protected health information. Your signature means that you are giving approval (authorization) for the use and disclosure of your protected health information for research purposes, as described in this form. You will be given a copy of this form to keep.

_____ _____

Signature of Research Participant (Date) Printed Name of Research Participant

_____ _____

Signature of Investigator Obtaining Approval (Date) Printed Name of Investigator

KESSLER FOUNDATION RESEARCH CENTER

NOTICE OF PRIVACY PRACTICES - HUMAN SUBJECT ASSURANCE FORM

IRB # E-700-11

Name of Research Study: **Visual Processing Speed in Multiple Sclerosis**

Name of Principal Investigator (complete printed name): Dr. Nancy Chiaravalloti,

Address of Principal Investigator (complete address): Kessler Foundation, 300 Executive Drive, Suite 70, West Orange, NJ 07052.

Future participation in research studies ***(please initial one):***

_____ Please contact me about participating in future studies. I understand that checking this space means that any researcher at Kessler Foundation Research Center may contact me about future research.

_____ Please DO NOT contact me about participating in future studies

This is to certify that I have received a Notice of Privacy Practices for the above named research protocol, pursuant to the Department of Health and Human Services Health Insurance Portability and Accountability Act (HIPAA) 45 CFR 164.520.

Subject Name	**Subject Signature**	**Date**
Witness Name	**Witness Signature**	**Date**

FORM INSTRUCTIONS:
NOPP policy (attached) should be discussed and a copy provided to subject; this Human Subject Assurance Form should be signed and kept in PI study files.