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Multiple sclerosis: Cognition and saccadic eye movements

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ABSTRACT

Ocular motor abnormalities are frequently reported in Multiple Sclerosis (MS), the most salient of which are well represented by the commonly used clinical measure, the EDSS. However, cognitive function, which is poorly represented by this scale, may also be ascertained from ocular motor measures, suggesting that an analysis of eye movements has the potential to extend and complement this more conventional measure. The generation of single and triple-step memory-guided saccades was investigated in 25 individuals with MS and a comparable number of neurologically healthy individuals matched for age and IQ. Experimental measures were correlated with a battery of neuropsychological tests evaluating attentional, working memory and executive processes, the cognitive domains most commonly compromised in MS.

For single memory-guided saccades, MS patients were less accurate and generated more erroneous responses to non-target stimuli. Saccadic latencies were also prolonged. For triple-step memory-guided saccades, MS patients were less accurate and more variable. A number of significant correlations were revealed between measures of each of these characteristics and scores on the range of neuropsychological assessments. These ocular motor measures demonstrate considerable sensitivity with respect to evaluating cognitive function in MS, particularly working memory and inhibitory control processes. This suggests that they could represent the foundation of a user-friendly surrogate marker of disease severity and progression in MS.

1. Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS), with no known cure. Pathologically, it is characterized by areas of demyelination and T-cell predominant perivascular inflammation in white matter (WM) regions, as well as more subtle and diffuse tissue damage in 'normal-appearing' WM and grey matter (GM) structures, demonstrating an important neurodegenerative component [1]. Ocular motor abnormalities are a common feature of MS, with several distinct ocular motor syndromes including fixation instability, internuclear ophthalmoplegia, impaired pursuit, and skew deviation [2]. These are largely consistent with the involvement of more eloquent sites, with the brainstem and cerebellum in particular, and have been shown to predict greater general disability, and a poorer prognosis in MS [3]. Due to the salience of these abnormalities, many are well represented by Kurtzke Functional Neurological Status (FSS) and Expanded Disability Status Scale (EDSS) scores [4], the most widely used method of quantifying disability in MS.

However, eye movement characteristics could provide considerable insight beyond the integrity of control circuits and descending motor pathways in MS. They could also provide a valuable resource with which to explore movement control more generally, particularly with respect to the cognitive control of behaviour (Leigh & Kennard, 2004). The cognitive control of eye movements is a burgeoning area of research, primarily because of the simplicity and depth of understanding of the ocular motor system, and the ease with which eye movements can be measured The ocular motor system is increasingly seen as a model motor system [5], and as Milea et al. (2005) propose, the knowledge acquired about the control of eye movements could be generalised to more complex behaviours such as attention (prioritisation of sensory input), inhibitory control, working memory, and decision-making processes [6]. Deficits in each of these domains represent some of the most debilitating cognitive changes found in MS [7,8], and are present in up to 70% of all cases [9]. Cognitive deficits encompass all disease stages and types of clinical course, and are even prevalent when diagnosis is only probable [10]. Unlike motor and sensory symptoms, cognitive changes are poorly represented by the EDSS.

Cognitive deficits in MS have been conventionally attributed to slowed conduction, a result of WM pathology [11–13], although correlations between cognitive status and T2-weighted MRI or microscopic tissue damage have been quite modest [12–16]. Diffuse

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WM damage does, however, correlate well with more complex cognitive processes which require communication across large-scale cortical networks [17]. Certainly connectivity is changed early on in the course of the disease [18], disrupting controlled information processing [19]. More recently, GM pathology has also been identified as a significant contributor to cognitive dysfunction, and irreversible axonal loss and cerebral atrophy have been found in the earliest stages of the disease [20–23].

Networks and structures implicated in a range of ocular motor behaviours are relatively well defined, including those that regulate control of memory-guided (MG) saccades, whereby saccades are directed to a previously illuminated stimulus following a predetermined delay. MG saccades provide a sensitive measure of working memory processes (as well as attention), which are disrupted early on in the course of disease in MS [24–26]. Any working memory task requires the synchronisation of long-distance connections between prefrontal, cingulate, and parietal regions, integrating complex information to generate appropriate responses. Such distributed systems are necessarily sensitive to diffuse WM and GM damage as found in MS [19].

The work presented here evaluates the control of single and triple-step MG saccades in patients with MS, correlating results with standardised neuropsychological measures of attention, working memory, and speed of information processing. Sartori and Eden (2006) have previously demonstrated the sensitivity of The Paced Auditory Serial Addition Task, the Symbol Digit Modalities Task, the California Verbal Learning Test, and the backwards digit span tests, in evaluating the cognitive status of MS patients [9]. If our ocular motor measures can be shown to demonstrate comparable sensitivity, these may provide the foundation of a user-friendly surrogate marker of disease severity and progression in MS, providing an assessment of motor, as well as cognitive function, both important components of the disease. Significantly, the Paced Auditory Serial Addition Task, which is considered the reference task for the cognitive evaluation of MS patients, is often poorly tolerated, generating considerable anxiety, resulting in non-compliance.

2. Methods

2.1. Participants

Twenty five patients meeting the McDonald criteria for MS participated in this study, 22 diagnosed as relapsing-remitting, and 3 as secondary progressive. Mean age was 40 years (range 24–58 years), mean disease duration was 62 months (range 4–164 months), and scores using the Expanded Disability Status Scale (EDSS) ranged from 0–5 (median score of 1). Nine of these patients had no clinical signs of MS (i.e. an EDSS score of 0). Twenty five age-matched healthy participants [mean age of 40 years (range 26–62 years)] served as a control group. Control subjects presented with no history of head injury, no central neurological disorder or psychiatric illness, and no regular intake of psychoactive drugs or history of drug abuse. Control and MS groups were comparable for IQ using the NART [27] (controls $M=116.60$, MS patients $M=114.38$), and depressive state using the Beck Depression Inventory (BDI) [28]; although 5 MS patients exhibited moderate symptoms of depressive illness (BDI scores between 0–18), scores were not significantly different to those of control participants and did not correlate with any experimental measure. Ethics approval was granted by the Melbourne Health Human Research Ethics Committee, and all participants gave their informed consent prior to inclusion in the study, in accordance with the Helsinki declaration. All MS patients continued with their normal medication regimen.

2.2. Equipment

Horizontal displacement of the eye was recorded using an IRIS infrared eye tracker (Skalar Medical, BV, Delft, The Netherlands) [29], with output sampled at 1 kHz, and recorded for off-line analysis using a customized program written in Matlab. Screen based stimuli were generated using E-Prime software, and displayed on a 21 inch monitor. Participants were seated in a darkened room, 840 mm directly in front of the monitor, with their heads stabilised using a bite bar. Test stimuli were presented on a black background and comprised green, red, or white target crosses measuring 30 mm x 30 mm, or a white centrally positioned re-fixation stimulus (square ring measuring 10 mm x 10 mm). Output from the eye tracker was displayed alongside a control signal generated by E-Prime, which indicated stimulus change. A photodiode was placed directly over a non-visible portion of the screen to concurrently record stimulus change in real-time.

2.3. Single memory guided saccades

Participants were asked to fixate a green cross presented at the centre of the screen for 1500 ms. A red cross was then presented concomitant with the green central cross at either 5° or 10° left or right of centre for 500 ms. Participants were asked not to look directly at the red cross, but to remember its spatial position. Following extinction of the red cross, the green fixation cross was present for a further 1500 ms or 2500 ms. Participants were instructed to move their eyes to the spatial position of the previously illuminated red cross as soon as the green fixation cross disappeared. A green cross was presented in the same location as the red cross for 1750 ms prior to allow participants to adjust their final eye positions, prior to appearing at centre to signify the onset of the next trial. The task included 48 trials (24 left and 24 right, balanced for 5° and 10° steps). Four practice trials familiarised the subject with the task prior to recording. Key measurements were saccade latency (ms), anticipatory errors (%; saccades made prior to the extinction of the green central cross), gain of the final eye position of the memory-guided saccade (prior to the appearance of the green eccentric cross correcting gaze position), gain of the final eye position (corrected saccade), and mean absolute position error.

2.4. Sequences of memory-guided saccades

This paradigm derives from that described by Heitger [30]. A green central fixation cross was firstly presented for 1000 ms, before jumping to three successive horizontal eccentric positions 3.3°, 6.7°, or 10° on either side of fixation, 2000 ms for each position. Each sequence ended at fixation. This task comprised six different sequences with four target positions (three steps left, right, and left over centre fixation, or right, left, right over centre fixation, and a return step to centre). Four practice sequences were presented in succession, with a 2000 ms break, prior to recording the memory-guided sequence. Throughout the practice trials, participants were required to follow the targets and memorise each position, its order, and timing within the sequence. A white fixation cross presented at centre for 500 ms initiated the memory guided sequence, where participants replicated the sequence in darkness as accurately as possible with respect to spatial position and timing. A new sequence was presented once participants had returned gaze to centre. Key measurements were gain of the final eye position and mean absolute position error. Both MS patients and control subject made relatively few directional errors which were excluded from the collated saccade data to avoid their contribution to measures of spatial (in)accuracy.

2.5. Neuropsychological tests

Attention, working memory, and speed of information processing were assessed using the Paced Auditory Serial Addition Task (PASAT) [31], the California Verbal Learning Test (CVLT) [32], Symbol Digit Modalities Test (SDMT) [33], and the backward digit span subtest derived from the Wechsler Adult Intelligence Scale (WAIS-III), as