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Note

Antisaccade performance in patients with multiple sclerosis

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ABSTRACT

Commonly used measures of disability in patients with Multiple sclerosis (MS) inadequately reflect disease severity and progression. Further, cognitive deficits experienced by up to 70% of patients, are poorly represented by these measures. Saccadic eye movements may provide a powerful tool for the analysis of cognitive changes in MS, providing a surrogate measure of performance that extends more conventional measures. The cognitive control of eye movements has not previously been investigated in patients with MS. We studied antisaccade (AS) performance in 25 patients with MS and compared the results with 25 age matched healthy controls, to evaluate the resolution of response conflict between volitional and automatic processes. Experimental measures were also correlated with a battery of neuropsychological tests evaluating attention, working memory and executive processes, the most commonly reported cognitive deficits in MS. Compared to controls, patients with MS generated significantly more prosaccade errors, and AS latencies were prolonged and more variable. Error rates correlated significantly with scores on the commonly used PASAT. MS patients also exhibited poor spatial accuracy, with mean absolute error significantly larger and more variable than control subjects. The sensitivity of this task in dissociating function in MS, as well as clear correlation with a key measure of cognition, suggests that eye movements, may provide a surrogate measure of cognitive function in MS, with the potential to sensitively assess disease severity and progression.

1. Introduction

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system characterised by diffuse tissue damage to both white and grey matter regions. Ocular motor abnormalities are a prominent feature of disease, with a number of stereotyped and easily recognised syndromes such as fixation instability, internuclear ophthalmoplegia and skew deviation (Frohman et al., 2005). These largely reflect pathology within the brainstem and cerebellum, and are well represented by the commonly used Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The EDSS, however, is largely dependent on pyramidal dysfunction and fails to adequately encompass the range of debilitating cognitive deficits that modulate motor behaviour and are an early feature in the course of disease in 40–70% of cases (Sartori and Edan, 2006).

We suggest that an evaluation of the higher-order, or cognitive control processes involved in generating eye

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movements may provide a sensitive method for assessing and monitoring patients with MS that extends this conventional measurement of function. Certainly, eye movement paradigms are increasingly used to probe the distributed cortical and subcortical systems involved in cognitive control processes, presenting a number of advantages over more conventional measures. The neural correlates of eye movements are well understood, translational models in non-human primates are readily available, and procedures are simple, brief, and well tolerated. Further, there is a considerable body of knowledge on eye movement performance in a range of psychiatric and neurological patient populations, providing a valuable starting point for comparison of a new patient group, such as MS.

We have previously established that patients with MS experience a number of difficulties generating memory-guided and endogenously cued saccades, with deficits correlating significantly with a number of neuropsychological measures (Fielding et al., 2009a, in press). The following study extends this work and evaluates performance by MS patients using the antisaccade (AS) task, a reliable and sensitive measure of cognitive function used extensively by neurologists, psychiatrists and psychologists over a range of neuropsychiatric populations (Hutton and Ettinger, 2006). This task requires the participant to refrain from reflexively responding to a peripheral target and instead direct gaze in the opposite direction. The inhibition of a pre-potent response and the ability to alter stimulus-response associations are both critical cognitive operations, primarily dependent upon the integrity of frontal and parietal regions. Performance over a number of neuropsychological tasks that sensitively reflect disease severity in MS, were also evaluated and correlated with our ocular motor measures to help validate our proposal.

2. Methods

2.1. Participants

Twenty five patients meeting the McDonald criteria for MS participated in this study [21 females, 4 males; mean age of 39.72 years (24–58); mean disease duration of 62.24 months (4–164); mean EDSS score of 1.7 (0–5)]. Twenty five healthy participants [22 females, 3 males; mean age 40.13 years (26–62)] reporting no history of neurological or psychiatric disorders, served as a control group. Control and MS groups were comparable for IQ using the National Adult Reading Test (NART) (Nelson, 1982) (controls $M = 116.60$, MS patients $M = 114.38$). 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 regime.

2.2. Equipment

Horizontal displacement of the eye was recorded using a Skalar IRIS infrared eye tracker (Skalar Medical, BV, Delft, The Netherlands), with output sampled at 1 kHz. Screen based stimuli were displayed on a 21 inch monitor (Mitsubishi Electric Corporation, Tokyo, Japan), and generated using E-Prime software (Psychology Software Tools, Inc, PA, USA). Participants were seated 840 mm directly in front of the monitor with their heads stabilized using a custom-made bite bar. Test stimuli were presented on a black background and comprised a green target (cross; 30 mm × 30 mm) presented centrally, 5° or 10° from centre in either hemifield or a white centrally positioned re-fixation stimulus (square ring, 10 mm × 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. Antisaccade task

Participants were firstly instructed to fixate a centrally positioned target. Following a period of either 1250 msec or 1600 msec, this target was extinguished coincident with the appearance of a peripheral target. Participants were instructed not to look at the peripheral target but to make a saccade in the opposite direction as quickly and accurately as possible, ending an equal distance from the centre of the screen. The peripheral target was extinguished after 1500 msec and a re-fixation stimulus, presented for 150 msec, redirected gaze back to centre prior to the onset of the next trial. The task included 48 trials (24 left, 24 right, balanced for 5° and 10° steps). The procedure was demonstrated to all participants, and a variable number of practice trials were presented prior to testing to ensure understanding of all task requirements.

Key measures were proportion of directional errors (incorrect saccade to peripheral target), AS latency (msec), latency of directional errors (msec; prosaccade), correction time for directional errors (msec; latency from end of erroneous prosaccade to initiation of corrective saccade), gain of the final eye position (EP_{final}/SP), and mean absolute position error $[(EP_{final} - SP)/SP] \times 100$, where Ep_{final} is the final eye position and SP is the stimulus position. While mean absolute position error quantifies the size of the error, final saccade gain is sensitive to the direction of error (Heitger et al., 2004). Initial saccade amplitude was not compared as eye movements were disconjugate for 15 out of the 25 MS patients. Adduction and/or abduction weakness and a corresponding overshoot of the contralateral eye is common in MS. Differences in the actual metrics of movement will be reported elsewhere.

Mean and variability (as measured by standard deviations) of saccadic latency, error and accuracy were analysed, comparing MS and control subjects using either *t*-tests or Mann–Whitney *U* tests where any violation of distribution assumptions was evident. Neuropsychological test scores for MS patients were analysed using Mann–Whitney *U* tests and correlated against ocular motor measures using Pearson's *r*.

2.4. Neuropsychological tests

Attention, working memory, and speed of information processing were assessed using the Paced Auditory Serial Addition Task (PASAT), the California Verbal Learning Test: learning stage (CVLT), Symbol Digit Modalities Test (SDMT), and the backward digit span subtest derived from the Wechsler Adult