Ocular fixation instabilities in motor neurone disease

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A marker of frontal lobe dysfunction?

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Abstract *Objective* Eye movements are classically felt to be spared in motor neurone disease (MND). Although a range of ocular motor disorders have been reported, no consistent pattern has been established. Disturbances of ocular fixation have been noted in MND; however, fixation has not yet been formally examined. With the recent characterization of ocular fixation using saccadic intrusion amplitude and fixation periods, we performed a cross-sectional study to examine for abnormalities of ocular fixation in non-dementing patients with MND. *Methods* A total of 44 patients and 45 controls were recruited. Fixation was examined using infra-red oculography and all subjects then underwent a neuropsychological evaluation. *Results* Saccadic intrusion amplitude was found to be greater in patients compared to controls and in particular, spinal-onset patients. Saccadic intrusion amplitude in patients correlated with neuropsychological measures sensitive to lesions of the frontal lobes. *Conclusions* This is the first study to identify abnormalities of fixation in MND and these results indicate that ocular fixation instabilities may be a marker of the sub-clinical frontal lobe dysfunction in MND. A longitudinal study to examine if saccadic intrusion amplitude deteriorates with time would be of interest as this could provide a quantifiable objective marker of disease progression.

Key words motor neurone disease · eye movements

Introduction

Eye movement examination can be a very helpful tool in the diagnosis of some neurological conditions and, using infra-red oculography, has the advantage of being non-invasive and easy to perform. With the lack of quantifiable objective measures of disease in MND, characteristic eye movement abnormalities could be of great use both diagnostically and in research. Although eye movements are classically spared in MND some patients have been reported with a range of ocular motor disorders including nystagmus, saccadic hypometria [28], slowed saccades [8, 33], increased saccadic latencies [25], decreased smooth pursuit gain [3, 23, 25, 32] and saccadic interruptions of smooth pursuit [20] although these studies were small and often predated the El Escorial criteria. The most comprehensive study to date [37], however, found increased antisaccadic error rates and latencies with relative preservation of reflexive saccades suggesting frontal lobe dysfunction. A disturbance of fixation was also noted and patients were found to have

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an increased frequency of saccadic interruptions compared to controls; however, only square wave jerks were recorded. A recent paper examining fixation in normal healthy subjects found that saccadic intrusions, present in all subjects, were composed not only of square wave jerks but saccadic intrusions of various formations (single saccadic pulses, double saccadic pulses as well as monophasic and biphasic square wave jerks) [1]. However, previous work from our laboratory found that many saccadic intrusions did not readily fit into the four groups and morphological classification was not felt to be useful [12]. Nonetheless, a study of saccadic intrusions in fixation must incorporate all types of saccadic intrusion and not just square wave jerks. The interruption of steady fixation with saccadic intrusions is common in normal subjects [1]; however, ocular fixation has not yet been formally examined in many disease populations including MND. Recently, work from our laboratory demonstrated that the ocular fixation system can be measured and characterized in terms of fixation periods and saccadic intrusion amplitude [12]. This method appears resistant to the effects of aging, a particular advantage in a patient population such as MND. Our objective was therefore to perform a cross-sectional observational study to examine for abnormalities of ocular fixation in patients with MND.

Methods

Patients and controls

The study was approved by the local ethics committee (Office for Research Ethics Committees in Northern Ireland, ORECNI) and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Inclusion criteria included MND patients as defined by the original El Escorial criteria [10] excluding 'ALS/MND plus' cases or those with associated dementia as defined by the Neary criteria [30]. Subjects were not on any medications known to affect eye movements nor had they any eye or brain conditions that would affect eye movements. All subjects had normal bedside ophthalmic examinations. Patients were alert and responsive during testing and displayed no clinical evidence of respiratory weakness or hypoxia. No patients required non-invasive positive pressure ventilation support. Patients were recruited from the Northern and Republic of Ireland MND registers. Control subjects were recruited via patients' spouses or carers, hospital staff and healthy volunteers. All patients and controls gave informed consent before inclusion into the study. Patients attended on one occasion to the Oculomotor Laboratory of the Neurophysiology Department, Royal Victoria Hospital, Belfast where clinical, demographic, neuropsychological and eye movement data were collected.

Demographic and clinical data

Basic demographic and clinical data were collected including age and sex to allow for matching between patients and controls. Patients received the Amyotrophic Lateral Sclerosis Functional Rating Scale revised (ALSFRSr) [14] and a separate bulbar score was recorded from a component of the questionnaire. Disease duration was defined as the time from symptom onset to the date of inclusion in the study. Disease onset was recorded for each patient as spinal- or bulbar-onset. If a patient presented with both they were categorised as bulbar-onset. All patients satisfied the original El Escorial criteria [10] and patients from all four categories (definite, probable, possible and suspected) were included. Suspected MND patients represent those with clinical evidence of lower motor neurone disease only. Although four patients with suspected MND were included, they all had progressed to at least possible MND by the end of the study.

Eye movement recording

Eye movements were recorded using the infra-red scalar limbus system (Skalar Medical Iris Infra-red Light Eye-Tracker Model 6500) which records up to ± 15 degrees in the horizontal plane. The output of the system was filtered at 100 Hz (–3 dB) and digitised to 12-bit resolution. Subjects were positioned in a hydraulic chair in the dark with their neck supported and their head immobilised with head tongs. Measurements were recorded from one eye only. The height of the chair was adjusted to ensure that the subjects' eyes were level with the target stimulus. The target stimulus used for calibration and each task was a square of light subtending an angle of 0.25 degrees projected on to a black tangential screen 1.5 m away from the subject. VSG Eyetrace data acquisition software developed by CRS (Cambridge Research Systems) was employed to collect and process the data. Two of our authors, RCMcG and RP, developed additional software to allow calculation of specific test parameters. Prior to the test, the equipment was calibrated to each subject. Data were stored in files in a password-protected computer.

Subjects were asked to fixate a central target composed of a red square for 60 s in darkness. For the second part of the task they were asked to fixate the same target for five seconds before the light was extinguished, at which point they were asked to continue to fixate on the place where the light had been for the remaining 55 s. Outcomes measured included geometric mean saccadic intrusion amplitude with the target on (GMSIA ON) and off (GMSIA OFF) and geometric mean fixation period with the target on (GMFP ON) and off (GMFP OFF). Both the saccadic intrusion amplitudes and fixation periods displayed positively skewed distributions and the geometric mean saccadic intrusion amplitude (GMSIA) and geometric mean fixation period (GMFP) were used to characterize the distributions. A fixation period was defined as an epoch of at least 35 ms in which the eye velocity did not exceed 30 degrees/s. Fixation period duration is determined in part by saccadic intrusion frequency but also by the temporal distribution of saccadic intrusions. Frequent clustered saccadic intrusions may result in different fixation periods from frequent unclustered saccadic intrusions. Potential saccadic intrusions were identified by the analysis software if the saccade lasted longer than 6 ms and exceeded 20 degrees/s and either accepted or rejected by the researcher. Thresholds were set such that only saccadic intrusions exceeding the background noise level were included. Details of our fixation analysis can be found in a previous publication [12]. Fig. 1 demonstrates a typical fixation trace highlighting saccadic intrusions and fixation periods.

Neuropsychological tests

A brief neuropsychological evaluation was undertaken to test a range of cognitive functions. Because of the suggestion of the involvement of the frontal lobe in a previous study of eye movements in MND [37] and because of the growing evidence of sub-clinical frontal lobe dysfunction in non-demented patients with MND [2, 4, 15, 17, 21, 24, 26, 35] tests sensitive to lesions of the frontal lobes were included. Abnormal verbal fluency has been the most consistent finding in neuropsychological analyses of non-demented MND patients [4, 17, 21, 24, 35]. A test of written (letter) verbal fluency employing the 'Verbal Fluency Index' [7] was administered to test executive functions. Subjects were given five minutes to write down a list of words beginning with the

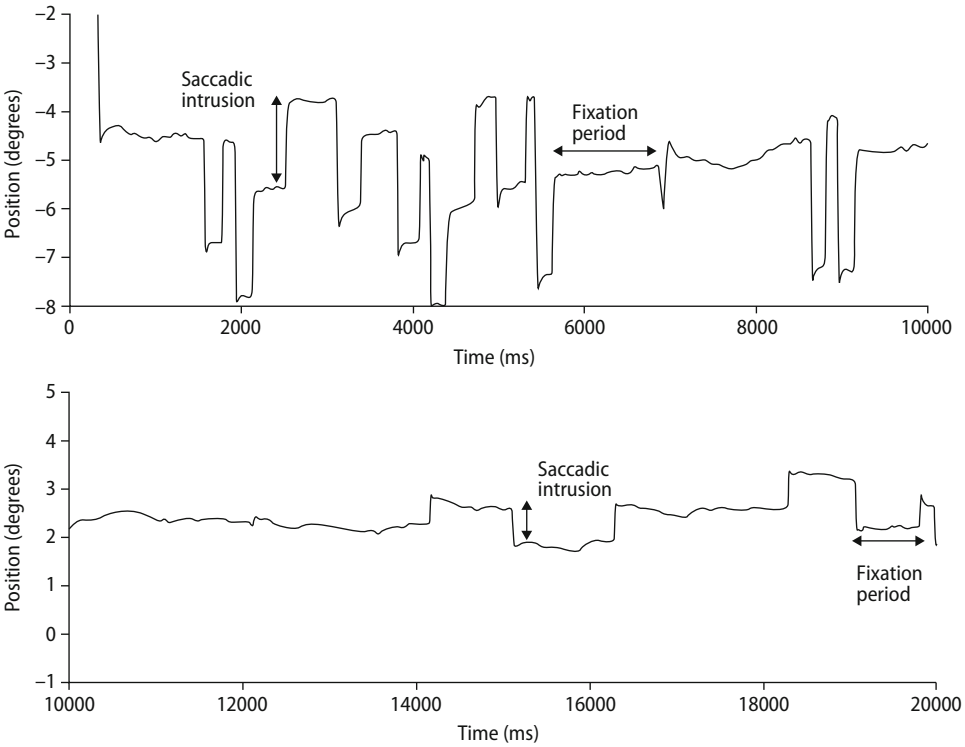

Fig. 1 Sample time series of fixation showing eye position from baseline (degrees) over time. Saccadic intrusions, measured by their amplitude (degrees) and fixation periods (milliseconds) are depicted by arrows. The top record is from a MND patient revealing larger amplitude saccadic intrusions compared to the record below from a control subject

letter 's', followed by four minutes to write down all four letter words beginning with 'c'. After each task each subject was asked to copy down all words that they had written and this was timed. The 'Verbal Fluency Index' (VFI) was designed in particular for patients with MND by accommodating for physical disability [7] and is an estimate of the average time taken to think of each word. Larger values of VFI represent more severe impairment. Verbal fluency relies on executive processes and is sensitive to lesions of the frontal lobe; however, IQ as well as language abilities can also affect verbal fluency. The 'National Adult Reading Test' (NART) [31], testing premorbid IQ, and the 'Graded Naming Task' (GNT) [27], testing naming and therefore language abilities, were administered with the VFI to account for this. A predicted full scale IQ based on the NART error score was also calculated. Language abnormalities, however, have been reported in some studies of non-demented ALS/MND patients [26] although less consistently than findings of executive dysfunction. A fMRI study by Abrahams et al. [6] found naming deficits indicating underlying language dysfunction associated with impaired activation of the inferior frontal lobe and occipitotemporal areas. The Color and Color-Word tasks from the STROOP neuropsychological screening test [38], a measure of visual attention and frontal lobe function, were also included. Two components ('Position Discrimination' and 'Number Location') of the 'Visual Object and Space Perception' (VOSP) test [39] were employed to help detect any visuospatial dysfunction that might affect ocular fixation. Anxiety or depressive states can affect those tasks requiring speed of thought and so the 'Hospital Anxiety and Depression Scale' (HADS) [40] was administered to all subjects. HADS-Anxiety represents the anxiety component of the questionnaire while HADS-Depression represents the depression component. A particular question within the HADS-Depression questionnaire asks if the person feels 'slowed down'. This would unfairly disadvantage MND patients and so results from all subjects were analysed without this component [7].

Statistical analyses

Because ocular fixation has not been formally examined in this patient population before, a power calculation could not be performed. Independent t tests and one-way analysis of variance were used to compare means between groups for fixation and neuropsychological test variables. Some data sets required log transformation to allow parametric testing because of skewed distributions. For non-normally distributed data, the Mann-Whitney U and Kruskal-Wallis H tests were used. Multiple linear regression was used to compare means between groups whilst adjusting for covariates. For any significant fixation or neuropsychological variable found between patients and controls, separate analyses were performed between clinical subgroups of patients and controls. Finally, correlation analyses were performed between any significant fixation variable and neuropsychological tests and clinical measures of disease. For data not normally distributed, the Spearman's rank correlation coefficient was used instead of the Pearson's coefficient. To examine for an association between two continuous variables while adjusting for covariates, multiple linear regression was employed. A proportion of patients were unable to perform certain neuropsychological tests due to anarthria or severe physical disability, and so patient numbers were smaller in some of the analyses performed.

Results

Demographic and clinical characteristics

A total of 44 patients (15 females, 29 males) and 45 controls (29 females, 16 males) were recruited. The groups were not matched for sex although there is no known reason for this to affect eye movement or cognitive test

results. The groups, however, were well matched for age with a mean age of 60 years for both groups. There were 7 definite, 19 probable, 14 possible and 4 suspected cases as defined by the original El Escorial criteria [10]. There were 30 spinal-onset compared to 14 bulbar-onset cases. All patients had normal eye movements on bedside testing. Mean and median disease duration was 52 and 39 months respectively. The mean ALSFRSr score for patients was 35 (range 18–47).

Fixation

GMSIA ON was found to be significantly larger in MND patients compared to controls; however, no difference was found in fixation periods (GMFP ON/OFF) between the groups (Table 1). These results indicate that MND patients have larger amplitude saccadic intrusions compared to controls. In addition, the size of saccadic intrusions during fixation of the visual target was found to be significantly different between the subgroups of MND and post hoc tests revealed that they were larger in 'spinal-onset' patients compared to controls (Bonferroni adjusted $p = 0.04$, $F = 3.37$, $df = 2$).

Neuropsychological tests

Neuropsychological test results comparing patients and controls are shown in Table 2. Significant differences were observed between groups for NART, predicted Full Scale IQ, GNT, VFI, STROOP and HADS-Depression. Not all patients were able to complete all tests due to varying levels of dysarthria and physical disability.

Patients displayed lower predicted full scale IQs compared to controls ($p = 0.003$). A difference was also found for GNT with patients displaying poorer naming/language abilities compared to controls ($p = 0.000$). Because IQ may affect a test of language, the analysis was repeated including NART as a covariate. A significant difference remained ($F = 4.99$, $df = 1$, $p = 0.03$). Significant differences were also observed between the groups for VFI (*s & c* letters) and VFI (*c* letters). As IQ and language are important contributors to a subject's ability to perform in a test of verbal fluency, VFI was re-examined including NART and GNT as covariates. A difference remained between the groups for VFI (*s & c* letters), with MND patients displaying poorer scores ($F = 4.09$, $df = 1$, $p = 0.047$). This means that it took longer for MND patients to think of words suggesting that they have deficits of executive functions. Further analysis was performed to examine for differences between VFI within different subgroups of MND. No significant differences were found for VFI when comparing spinal- and bulbar-onset MND patients with controls. VFI did not correlate with any measures of clinical disease (ALSFRSr, ALSFRSr bulbar or disease duration). When analysing STROOP and VOSP between the groups, data were not normally distributed and analysis required non-parametric testing which precludes the inclusion of covariates. Nonetheless using the Mann-Whitney test a difference was observed between the groups for STROOP ($p < 0.02$) indicating that patients had poorer attention than controls, suggesting frontal lobe dysfunction. No significance difference, however, was observed between the groups for VOSP. Although a statistically significant difference was found between the groups for HADS-Depression, scores in both groups were within normal limits.

Table 1 Fixation data

	MND group (n = 44)	Control group (n = 45)	P-value
GMSIA ON	0.64 (0.39)	0.48 (0.33)	**0.01**
GMSIA OFF	0.85 (0.47)	0.81 (0.77)	0.15
GMFP ON	185.3 (138.6)	194.2 (153.9)	0.98
GMFP OFF	188.9 (180.5)	209.7 (157.3)	0.41

Means and standard deviations are presented.
n number of subjects; *GMSIA ON* Geometric mean saccadic intrusion amplitude with the target stimulus on (degrees); *GMSIA OFF* Geometric mean saccadic intrusion amplitude with the target stimulus off (degrees); *GMFP ON* Geometric mean fixation period with the target stimulus on (ms); *GMFP OFF* Geometric mean fixation period with the target stimulus off (ms)

Table 2 Neuropsychological data

	MND group		Control group		P-value
	Mean (SD)	N	Mean (SD)	N	
NART	25.5 (9.8)	39	32.8 (11.2)	45	**0.002**
Predicted Full Scale IQ	100.4 (12.2)	39	109.3 (13.8)	45	**0.003**
GNT	17.2 (6.0)	42	21.6 (4.6)	45	**0.000**
VFI (*s & c* letters)	15.1 (16.6)	30	9.4 (8.1)	45	**0.01**
VFI (*s* letters)	10.7 (11.3)	30	6.7 (6.3)	45	0.06
VFI (*c* letters)	31.6 (42.7)	30	20.3 (35.1)	45	**0.02**
STROOP	35.1 (23.2)	36	23.6 (24.7)	45	**0.02***
VOSP	27.2 (2.4)	43	27.5 (2.1)	45	0.35*
HADS -Anxiety	7.5 (3.2)	43	7.2 (3.2)	45	0.76
HADS-Depression	3.9 (2.6)	43	2.3 (2.2)	45	**0.004**

SD Standard deviation; *n* number of subjects; *NART* National Adult Reading Test (maximum score 50); *VFI* Verbal Fluency Index (seconds); *GNT* Graded Naming Task (maximum score 30); *VOSP* Visual Object and Space Perception test (maximum score 30 representing subtests 'Position Discrimination' and 'Number Location'); *HADS* Hospital Anxiety and Depression Scale (Maximum score for HADS-Anxiety is 21 and for HADS-Depression is 18).
Independent T Test used except where specified.
* Mann-Whitney Test

Correlations

Analyses were performed on patients to establish if GMSIA ON correlated with any neuropsychological tests or measures of clinical disease. Only those patients who were able to provide relevant neuropsychological data could be analysed. Significant correlations were found between GMSIA ON and tests sensitive to lesions of the frontal lobes. These included VFI (*s* letters) and STROOP with a borderline significant correlation found for VFI (*s & c* letters) (Table 3). As saccadic intrusion amplitude increased scores for VFI and STROOP also increased, representing a poorer performance on these tests. VFI, as discussed previously, may be affected by IQ and language and a multiple regression analysis was then performed between GMSIA ON and VFI including NART and GNT as covariates. The covariates were not found to significantly affect the model, however, and so were not included in the analysis. Non-parametric testing was employed for STROOP precluding the inclusion of NART as a covariate to adjust for IQ. Fig. 2 displays the correlation between GMSIA ON and VFI (*s* letters). The graph reveals four outlying data points that if removed might appear to significantly affect the correlation, and so these data were rechecked to ensure that the relationship found was valid. No correlation was found between GMSIA ON and GNT, VOSP or HADS. As for STROOP a non-parametric correlation analyses was performed for VOSP precluding the incorporation of NART as a covariate to adjust for IQ. No correlation was noted between GMSIA ON and clinical measures of disease (Table 3).

Table 3 Correlation analyses between GMSIA ON and neuropsychological and clinical measures in MND patients

Neuropsychological tests	Pearson's correlation coefficient
VFI, *s & c* letters (n = 30)	r = 0.34 p = 0.07
VFI, *s* letters (n = 30)	**r = 0.41 p = 0.03**
VFI, *c* letters (n = 30)	r = 0.14 p = 0.46
GNT (n = 42)	r = –0.14 p = 0.4
STROOP (n = 36)	**r = 0.43* p = 0.01**
VOSP (n = 43)	r = –0.14* p = 0.38
Clinical measures of disease	**Pearson's correlation coefficient**
ALSFRSr (n = 43)	r = –0.19 p = 0.21
ALSFRS bulbar score (n = 43)	r = –0.03* p = 0.83
Disease duration, months (n = 44)	r = 0.03 p = 0.87
Estimated disease progression (n = 43) = (48 – ALSFRSr)/Disease duration	r = 0.12 p = 0.44

* Spearman's correlation coefficient
n number of subjects; *ALSFRSr* Amyotrophic Lateral Sclerosis Functional Rating Scale revised

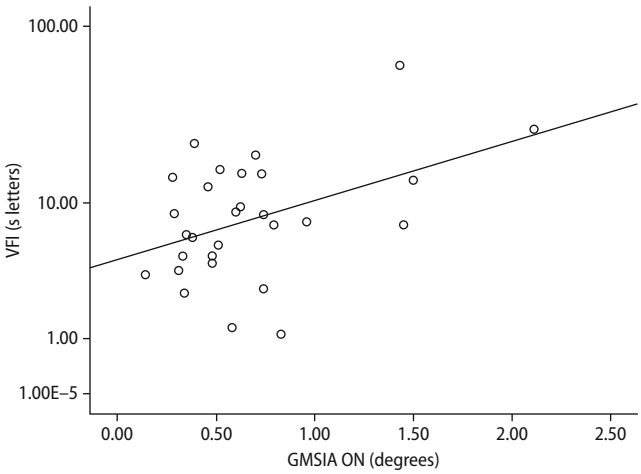

Fig. 2 Scatter plot highlighting the correlation between GMSIA ON and VFI (*s* letters). Regression coefficient, R = 0.33. *GMSIA ON* Geometric mean saccadic intrusion amplitude with the target stimulus on (degrees); *VFI* Verbal Fluency Index (seconds)

Discussion

The size of saccadic intrusions during fixation of the visual target were found to be larger in MND patients (p = 0.01) compared to controls. In particular, they were found to be larger in spinal-onset patients compared to controls (p = 0.04). Although a previous study [37] found an increase in the number of saccadic intrusions during fixation in patients with MND, only square wave jerks were included. Square wave jerks are only a component of all the small involuntary saccades that intrude on fixation [1] and therefore their study cannot be a true reflection of fixation in MND. The size of saccadic intrusions when fixating without a visual target were not found to be significantly different between patients and controls and this may be due to the fact that the amplitude of saccadic intrusions normally increases when the stimulus is extinguished [12, 18, 19], therefore possibly reducing the difference between the groups.

Patients demonstrated poorer scores on tests of executive function and attention, sensitive to lesions of the frontal lobes. These findings are consistent with the subclinical frontal lobe dysfunction that has been discovered over recent years in non-demented MND patients [2, 4, 15, 17, 21, 24, 26, 35]. Abnormal verbal fluency has been the most consistent finding in neuropsychological analyses of non-demented MND patients reported in the literature [4, 7, 17, 21, 24, 35]. Functional brain imaging studies have found correlations between reduced uptake or activation of the frontal lobes and cognitive impairment in patients with MND [2, 5, 6, 21]. Two studies using positron emission tomography looked in particular at verbal fluency and found that ALS/MND patients with impaired verbal fluency showed reduced

activation in areas along a thalamo-frontal pathway [5, 21]. Similarly, a functional magnetic resonance imaging study of verbal fluency in patients with ALS/MND found significantly reduced activation in the middle and inferior frontal gyri as well as the anterior cingulate gyrus and regions of the parietal and temporal lobes [6].

Importantly, the size of saccadic intrusions during fixation of the visual target was found to significantly correlate with the two neuropsychological measures which are sensitive to lesions of the frontal lobes. As saccadic intrusion increased, VFI and STROOP scores increased indicating that increased saccadic intrusion amplitude correlated with increased impairment. No correlation was observed with the VOSP subtests of occipitoparietal function.

The neuropathological substrate that leads to increased saccadic intrusion amplitude seen in patients with MND is not known. In MND the abnormal fixation may be associated with sub-clinical frontal lobe dysfunction, although functional imaging studies of fixation have been conflicting. Two studies comparing the fixation of a central target with eyes open in darkness (effectively simulating the difference between saccadic intrusion amplitude with the visual target light on or off) have been performed on healthy volunteers. One positron emission tomography study [34] found bilateral activations of the frontal eye fields and intraparietal sulcus as well as activations of the right frontal cortex when comparing patients fixating a central target compared to eyes open in darkness, while a functional magnetic resonance imaging study [16] found increases in occipito-temporal areas instead. Saccadic intrusions are thought to be generated from the saccadic system due to their similarity to saccade main sequence plots [12] and results from lesional studies have suggested that the rostral superior colliculus and basal ganglia both appear to have a role to play in maintaining fixation and inhibiting unwanted saccades.

Irrepressible saccades were reported to have been observed in a rhesus monkey caused by a stroke that involved the rostral superior colliculus along with its commissure and with minor invasion of the periaquaductal gray and adjacent mesencephalic reticular formation [13]. This was consistent with the results from a physiological study on a monkey [29] where a subset of neurons in the rostral pole of the superior colliculus, when subjected to inhibition using a pharmacological GABA agonist, caused unwanted saccadic eye movements. Pallidotomy in Parkinson's disease was also found to increase the number of saccadic intrusions (albeit square wave jerks) intruding on fixation [9]. The defect in our MND patients, however, is not necessarily an increased frequency of saccadic intrusions but rather higher amplitude saccadic intrusions. To the authors knowledge no literature exists to aid in the identification of the neural substrate of this state. If the cause of increased saccadic intrusion amplitude lies somewhere within the structures responsible for controlling the saccadic system and is not at the level of the superior colliculus or below, one could propose that the defect lies somewhere along a frontal-collicular pathway. This theory is consistent with the positive correlation found between the size of saccadic intrusion with the visual target and VFI. One other area, namely the cerebellum, warrants discussion in attempts to explain the observed disturbance of fixation. The cerebellum plays an important role in maintaining the accuracy of saccades [22] and saccadic intrusions have been noted in certain cerebellar syndromes [11, 36]. Interestingly, memantine, an NMDA antagonist, suppressed saccadic intrusions in two patients with spinocerebellar ataxia with saccadic intrusions [36]. It was assumed that the disturbance of fixation was due to disease of the cerebellar cortex, reducing the inhibition of the deep cerebellar nuclei when signals were presented by the mossy fibres. Because NMDA receptors are found at mossy fibre synapses it was postulated that memantine reduced mossy fibre input and therefore unnecessary saccadic intrusions. It had a less significant effect on saccadic intrusion amplitude, however, which was the predominant abnormality in our study.

In summary, our findings support the theory that ocular fixation instabilities, by way of increased saccadic intrusion amplitude, are a marker of the sub-clinical frontal lobe dysfunction in MND. This work lends further support to the increasing evidence of sub-clinical frontal lobe dysfunction in MND and may allow saccadic intrusion amplitude to be used as an oculomotor marker for such. This is the first study to document the finding of abnormal fixation in non-demented patients with MND. A longitudinal study to examine if saccadic intrusion amplitude deteriorates with time would be of significant interest due to the current lack of quantifiable objective markers of disease.

Conflict of interest The authors declare no conflict of interest.

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