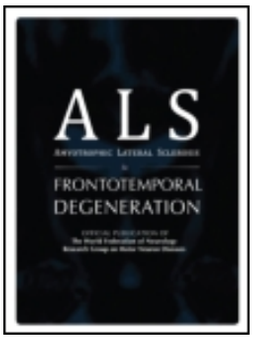

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ORIGINAL ARTICLE

Early saccades in amyotrophic lateral sclerosis

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Abstract

Our objective was to correlate saccadic abnormalities, including early saccades, in patients with amyotrophic lateral sclerosis (ALS) with measures of motor and functional impairment. A portable saccadometer was used to record saccades in ALS patients and control subjects. The linear approach to threshold with ergodic rate model was used to characterize saccades, including sub-populations of early saccades. Patients with established cognitive impairment or frontotemporal dementia were excluded. Limb-onset (Limb ALS) and bulbar-onset (Bulbar ALS) patient groups were compared and saccadic abnormalities were correlated with measures of motor and functional impairment. In total, 48 participants were included in the study; 24 patients with ALS (15 males, 9 females; mean age 57.0 +/− 13.9 years; mean symptom duration 22.4 +/− 16.3 months, of whom 62.5% had Limb ALS) and 24 age-matched controls. Early saccades were increased in both Limb ALS and Bulbar ALS patients, but other saccadic parameters were normal in ALS. Saccadic abnormalities did not correlate with motor or functional impairment. In conclusion, ALS patients show increased early saccades, but exhibit no significant differences across ALS phenotypes.

Key words: *ALS, saccades, early saccades*

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive deterioration of upper and lower motor neurons (1). Traditionally considered a pure motor disorder, extramotor features have been increasingly recognized (2–5). In particular, the relationship of saccadic abnormalities to clinical features remains controversial, with a previous study reporting more significant abnormalities in patients with bulbar-onset disease (Bulbar ALS) compared to those with limb-onset disease (Limb ALS) (4).

Given the close proximity of the cortical structures involved in saccade initiation (6,7) to the primary motor cortex, a major locus of pathology in ALS (8), abnormalities of eye movements may seem unsurprising. Nonetheless, previous studies of saccadic eye movements in ALS have reported conflicting results, probably reflecting the different approaches used to analyse saccadic recordings. In particular, marked variability in saccadic latency from one trial to the next has not always been appreciated.

One fundamental characteristic of saccadic eye movements is the marked variability in saccadic latency from one individual saccade to the next, which is observed in both normal controls and disease states (9,10). Such variability between saccades may reflect underlying decision-making processes prior to saccade onset (11). Given such variability, an analytical approach that takes the whole distribution of latencies into account is critical to avoid obscuring subtle differences from one subject to another by considering only abstracted values such as the mean latency of a series of saccadic recordings.

The LATER model (linear approach to threshold with ergodic rate) was developed specifically to examine whole distributions of saccadic latencies and allows detailed analysis of latency variability from one saccade to the next (11,12). The LATER model conceptualizes the decision-making process prior to the onset of an individual saccade as a 'rise to threshold' from a baseline level of expectation to a threshold at which the decision to generate a saccade is reached. The rate

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at which this process occurs varies randomly from one individual saccade to another, and is reflected in the individual saccadic latencies; a faster decision-making process results in a shorter saccadic latency. As such, the rate of decision-making immediately prior to a particular saccade can be thought of as the reciprocal of saccadic latency. Latency distributions can be elegantly demonstrated on a reciprobit plot, which plots reciprocal latency against cumulative probability. When plotted in this way, a straight line of best fit accurately describes the main distribution of saccadic latencies (Figure 1, and Supplementary material that is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/21678421.2013.783077).

Occasionally, a small sub-population of early saccades with unexpectedly short latencies (12) is evident on reciprobit plots. Early saccades are more common when cortical influence on saccadic initiation is impaired through distracting, cognitively demanding tasks, or under conditions of urgency (12–14). Alternatively, an increased proportion of early saccades could reflect cognitive dysfunction. In support of this hypothesis, an increased proportion of early saccades was recently demonstrated in frontotemporal dementia (15), which shares neuropsychological (3) and clinicopathological features with ALS (1).

The present study hypothesized that saccadic latency would be abnormal in ALS, as measured using the LATER model. In particular, it was hypothesized that the incidence of early saccades in ALS would be increased compared to a control group. Furthermore, the study sought to establish whether saccadic abnormalities were more severe in patients with Bulbar ALS than those with Limb ALS. Finally, given the proximity of the FEF and other structures involved in saccadic initiation to the primary motor cortex, the study examined the relationship between saccadic eye movements and motor impairment in ALS.

Materials and methods

Participants

We recruited patients with a prior diagnosis of ALS from a multidisciplinary motor neuron disease clinic, after written informed consent and institutional ethics approval. The diagnosis of ALS was made according to the El Escorial and Awaji criteria (16). Patients were further classified as either Limb ALS or Bulbar ALS according to the symptoms that predominated at presentation. ALS patients were screened for cognitive impairment, and those who met the diagnostic criteria for FTD (17) were excluded from the study. Healthy age- and gender-matched controls were included for comparison.

Clinical assessments

Patients with ALS underwent a standardized clinical assessment. The presence of fasciculations and muscle wasting was systemically explored in multiple bulbar and limb regions, as described in detail elsewhere (18). Any degree of wasting or fasciculations was regarded as clinically significant and recorded as either 'present' or 'absent'. Limb power was assessed and graded according to the Medical Research Council (MRC) grading system; individual muscle grades were added to calculate the MRC sum score (MRCSS) for each patient (19). The MRCSS yields a total score of 60 in normal subjects. Motor functional impairment was graded using the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised

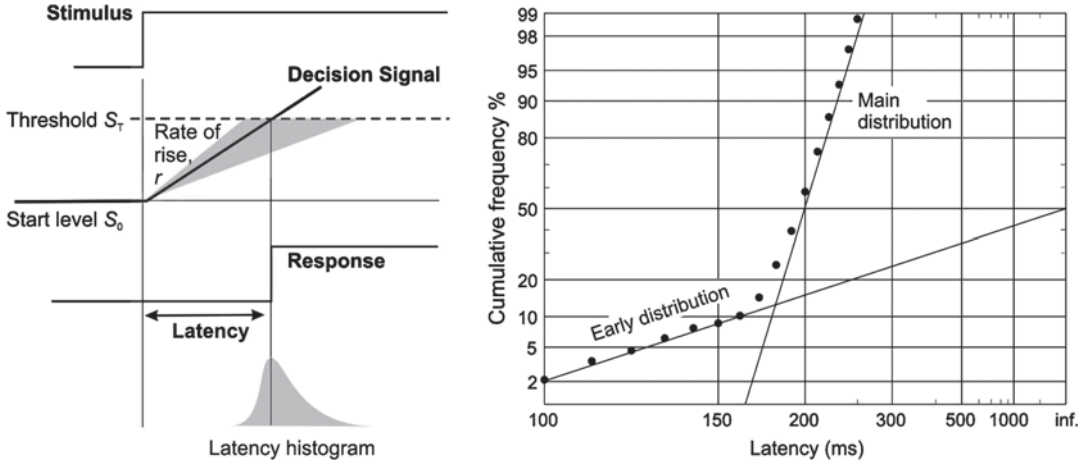

Figure 1. The LATER model. Left, stimulus onset causes a decision signal to rise linearly at a rate r from an initial value S_0 until it reaches a threshold S_T, at which point it triggers a response. On different trials, r varies as a Gaussian random variate, generating a skewed distribution of latencies. Right, as a result, if a histogram is plotted as a cumulative distribution on a probability scale, as a function of reciprocal latency, in general a straight line is obtained ('Main distribution'). In certain circumstances a sub-population of early saccades may be seen, that normally lies on a different straight line of shallower slope ('Early distribution'). See Supplementary material that is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/21678421.2013.783077 for more details.

(ALSFRS-R) (20). The ALSFRS-R total score as well as bulbar, fine motor, gross motor and respiratory sub-scores were calculated for each ALS patient. Finally, to estimate the rate of disease progression, the difference in the measured ALSFRS-R total from a normal value of 48 was divided by the disease duration, recorded in months (21).

Saccadometry

We used a Saccadometer Advanced (Ober Consulting, Poland) (22) to perform saccadometry. This is a miniature device that records saccadic eye movements in the horizontal plane with 1 kHz sampling frequency, by means of infrared scleral reflectance (22). Head restraint is not required as the device is secured to the subject's forehead by an elastic strap. Lasers mounted on the device project target stimuli in front of the subject. Experiments were performed in a quiet room with the target stimuli projected on a blank wall or screen 2.5 m in front of the seated subject. The subject carried out a visually evoked step task, in which, after a random delay in the range 0.5–1.5 s, an initial central fixation target was replaced with a peripheral target at 10 degrees randomly to the right or left of the midline. The subject was instructed to follow the target with their eyes, and after each saccade the target returned to the centre for the start of the next trial; a run of 50 such trials typically took two or three minutes to complete. Mean saccadic velocity was measured by a second experiment that required the subject to look between two alternating peripheral targets 20 degrees apart in the horizontal plane. Calibration was performed automatically before each run. We chose a step task of this kind (sometimes – misleadingly – called 'reflexive') because in normal subjects it does not typically generate many early saccades (15).

A third experiment was a cued anti-saccade task. Each trial began with dual central targets, one red and one green, presented centrally with a small vertical offset. A single red or green central target was then presented with a simultaneous right or left peripheral target. Subjects were instructed to look at the peripheral target if the single central target was green, and look away from the peripheral target if the single central target was red. Each individual trial was followed by a gap of 750 ms, following which both central targets would reappear. Due to the complexity of the task, it was demonstrated to each subject prior to commencement to ensure that the instructions were understood correctly.

For all experiments, LatencyMeter (Ober Consulting, Poznan, Version 4.9) was used to perform the initial analysis of data downloaded from the saccadometer. LatencyMeter employed a statistical analysis of the position and velocity profile of each individual trace to identify and exclude invalid traces, such as those confounded by saccadic intrusions resulting from impaired fixation, although in practice very few traces were identified as invalid.

Statistical analysis

The LATER model was used to estimate parameters describing the latency distributions of individual participants, parameters that reflect fundamental aspects of the underlying cerebral decision processes (23). The parameter μ represents the mean rate of rise of the principal decision process, and its standard deviation is given by σ. Early saccades can be considered to be due to a competing process of the same kind, having a mean of zero but a large standard deviation, σ_E; an increased σ_E indicates an increased incidence of early saccades. We used Saccadic Programming and Instrumentation Computer (SPIC) software (http://www.cudos.ac.uk/spic.html) (24) to estimate LATER parameters for the step task, by minimization of the Kolmogorov-Smirnov one-sample statistic (25).

Statistical analysis was performed by a single author (JRB) using the Statistical Package for Social Sciences (SPSS, IBM Corp, version 20.0). ALS patients were first compared to controls. Subsequently, Limb ALS and Bulbar ALS groups were compared. Finally, clinical measures of motor involvement and functional impairment were correlated with measures of saccadic eye movements using Spearman bivariate correlations. Continuous variables were analysed using analysis of variance (ANOVA) when normally distributed, or the Kruskal-Wallis test when non-normally distributed. Pairwise comparisons were performed using the independent samples *t*-test when continuous variables were normally distributed and the Mann-Whitney test when non-normally distributed. Categorical data were analysed using the χ^2 test.

Results

Patient demographics and clinical features

In total, 48 participants were included in the study, 24 patients with ALS and 24 age-matched control subjects. The mean age of ALS patients was 57.0 +/− 13.9 years compared to 59.8 +/− 15.8 years for controls. Of the ALS patient cohort, 62.5% were male compared to 41.7% of the controls ($p = 0.15$), and the mean symptom duration at the time of study for ALS patients was 22.4 +/− 16.3 months. The mean rate of progression was 0.56 +/− 0.43 ALSFRS-R points per month. Limb ALS accounted for 62.5% of ALS cases and the rest were classified as Bulbar ALS. Overall, ALS patients demonstrated at least moderate motor weakness and functional impairment, as reflected in a reduced mean MRCSS total and reduced ALSFRS-R total (See Supplementary Table I, which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/21678421.2013.783077).

Table I. Clinical features of Limb ALS and Bulbar ALS patients. Limb ALS patients had more significant limb wasting, fasciculations, weakness, and motor functional impairment. In contrast, Bulbar ALS patients had significantly more dysarthria and bulbar functional impairment. The degree of respiratory impairment was negligible in both groups.

	Limb ALS	Bulbar ALS	*p*-value
Number of patients	15	9	
ALSFRS (mean +/− SD)			
Bulbar	10.4 +/−0.3	7.2 +/−0.8	<0.001
Fine motor	6.5 +/−0.9	11.0 +/−0.6	<0.001
Gross motor	8.4 +/−0.8	10.7 +/−0.6	<0.05
Respiratory	11.5 +/−0.2	11.8 +/−0.1	NS
Total	36.9 +/−1.4	40.7 +/−1.9	<0.05
Wasting (% patients)	15 (100%)	7 (77.8%)	0.06
Fasciculations (% patients)	13 (86.7%)	7 (77.8%)	NS
MRCSS	50.1 +/−2.4	59.8 +/−0.2	<0.001
Dysarthria			
None	6 (40.0%)	0	<0.05
Flaccid	5 (33.3%)	0	
Mixed	4 (26.7%)	6 (66.7%)	
Spastic	0	3 (33.3%)	

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; MRCSS: Medical Research Council Sum Score. All continuous variables are presented as mean +/− standard error of the mean.

All patients completed the three saccadometry experiments, regardless of the severity of functional impairment. Typically, saccadometry required less than 15 min in each patient, even when allowing for calibration and fitting of the device, and explanation of the tasks.

Clinical features: Bulbar ALS vs. Limb ALS

As might have been expected, Limb ALS patients demonstrated significantly greater limb weakness than Bulbar ALS patients (Table I), as reflected by a reduced MRCSS (Limb ALS 50.1 +/− 9.2; Bulbar ALS 59.8 +/− 0.07, $p < 0.001$). Both ALS subgroups were functionally impaired, but the Limb ALS group was slightly more impaired functionally than the Bulbar ALS group, reflected by a reduced ALS-FRS-R total (Limb ALS 36.9 +/− 5.3; Bulbar ALS 40.7 +/− 5.8, $p < 0.05$). The pattern of motor involvement was reflected in the ALSFRS-R sub-scores. For example, Limb ALS patients had a greater reduction in the fine motor sub-score (Limb ALS 6.5 +/− 3.6; Bulbar ALS 11.0 +/− 1.7, $p < 0.001$), but Bulbar ALS patients had a greater reduction in the bulbar sub-score (Limb ALS 10.4 +/− 1.3; Bulbar ALS 7.2 +/− 2.5, $p < 0.001$). While dysarthria was more common in Bulbar ALS patients, 60% of Limb ALS cases also had some degree of speech disturbance.

Saccadometry

An increased incidence of early saccades was identified in ALS patients, reflected in a highly significant increase in σ_E (ALS 4.4 +/− 2.6; controls 1.3 +/− 2.5, $p < 0.001$, Figure 3). Interestingly, a trend for correlation between the frequency of early saccades and rate of ALSFRS decline was detected ($r = 0.37$, $p = 0.07$). As expected, marked variability in saccadic latencies was detected from one saccade to the next in control subjects and ALS patients. For example, there was marked increase from the minimum saccadic latency (ALS 91.8 +/− 4.7 ms, controls 100.8 +/− 7.4 ms, NS) to the maximum saccadic latency (ALS 694.3 +/− 86.4 ms, controls 643.3 +/− 98.3 ms, NS) in both groups. Importantly, neither median saccadic latency nor μ differed sig-

Table II. Saccadometry in ALS patients. The proportion of early saccades was increased in ALS, reflected in an increased σ_E, compared to controls. The saccadic latency, mean velocity, and rate of preceding decision-making speed (μ) did not differ between ALS patients and controls.

	ALS	Control	*p*-value
Number of patients	24	24	
Age (years)	57.0 +/− 2.8	59.8 +/− 3.2	NS
Male gender (%)	15 (62.5%)	10 (41.7%)	NS
Right-hand dominant (%)	23 (95.8%)	22 (91.7%)	NS
Latency (ms)			
Median	200.7 +/− 6.5	190.3 +/− 7.9	NS
Minimum	91.8 +/− 4.7	100.8 +/− 7.4	NS
Maximum	694.3 +/− 86.4	643.3 +/− 98.3	NS
Velocity (deg/sec)			
Peak	660.4 +/− 54.3	705.0 +/− 50.7	
Mean	527.5 +/− 38.1	535.0 +/− 28.1	NS
LATER parameters			
μ	5.1 +/− 0.2	5.5 +/− 0.3	NS
σ	1.0 +/− 0.1	1.1 +/− 0.1	NS
σ_E	4.4 +/− 0.5	1.3 +/− 0.5	<0.001
Anti-saccade performance			
% correct	68.0 +/− 2.6	68.7 +/− 3.1	NS

LATER: Linear Approach To Ergodic Rate model. All continuous variables are presented as mean +/− standard error of the mean.

Table III. Saccadometry in Limb ALS and Bulbar ALS. Both the Limb ALS and Bulbar ALS groups had a significantly increased proportion of early saccades, as reflected by an increased σ_E, compared to controls. The saccadic latency, mean velocity, and rate of preceding decision-making speed (μ) did not differ between ALS patients and controls.

	Limb ALS	Bulbar ALS	Control	*p*-value
Number of patients	15	9	24	
Age (years)	55.7+/−3.9	59.1+/−4.1	59.8+/−3.2	NS
Male gender (%)	11 (73.3%)	4 (44.4%)	10 (41.7%)	NS
Right-hand dominant (%)	15 (100%)	8 (88.9%)	22 (91.7%)	NS
Latency (ms +/− SD)				
Median	200.2+/−7.7	201.5+/−12.3	190.3+/−7.9	NS
Velocity (deg/sec)				
Peak	681.4+/−77.8	625.4+/−68.2	705.0+/−50.7	
Mean	541.5+/−56.6	504.1+/−45.9	535.0+/−28.1	NS
LATER parameters				
μ	5.1+/−0.2	5.1+/−0.3	5.5+/−0.3	NS
σ	1.0+/−0.1	1.0+/−0.1	1.1+/−0.1	NS
σ_E	4.7+/−0.6	3.9+/−1.0	1.3+/−0.5	<0.001[a,b]
Anti-saccade performance				
% correct	66.9+/−3.7	70.0+/−3.2	68.7+/−3.1	NS

All continuous variables are presented as mean +/− standard error of the mean.
[a]Bulbar ALS vs. controls, $p<0.05$.
[b]Limb ALS vs. controls, $p<0.001$.

nificantly between ALS patients and controls, nor did peak saccadic velocity on the second experiment or the error rate on the anti-saccade task (Table II).

Saccadometry: Bulbar ALS vs. Limb ALS

The saccadometry parameters were similar across Limb ALS and Bulbar ALS groups (See Table III). Specifically, the incidence of early saccades, as indicated by an increased σ_E, was increased in both Limb ALS ($p<0.001$) and Bulbar ALS ($p<0.05$) compared to controls (Figure 2A, B), but did not differ between the two ALS sub-groups (Limb ALS 4.7 +/− 2.3; Bulbar ALS 3.9 +/− 3.1, $p=0.73$); neither did any of the other parameters, including anti-saccade error rate.

Correlation of saccadic parameters and motor features

Despite the increase in early saccades in both Bulbar ALS and Limb ALS phenotypes, this increase did not correlate significantly with measures of motor or functional impairment. Specifically, increased σ_E did not correlate significantly with motor weakness, as measured by a reduced MRCSS score ($r=-0.05$, $p=0.82$), or with functional impairment reflected in a reduced ALSFRS-R total ($r=-0.26$, $p=0.22$). Similarly, there were no significant correlations between the decision-making speed (as reflected by μ), or variability in decision-making speed (as reflected by σ), and MRCSS total or ALSFRS-R total. Of further interest, there was no significant correlation between measures of saccadic eye movements and bulbar dysfunction, as measured by the ALSFRS-R Bulbar sub-score.

Discussion

The present study has demonstrated that the distribution of saccadic latency is abnormal in ALS. Specifically, we found an increase in the incidence of early saccades in ALS compared with controls. An

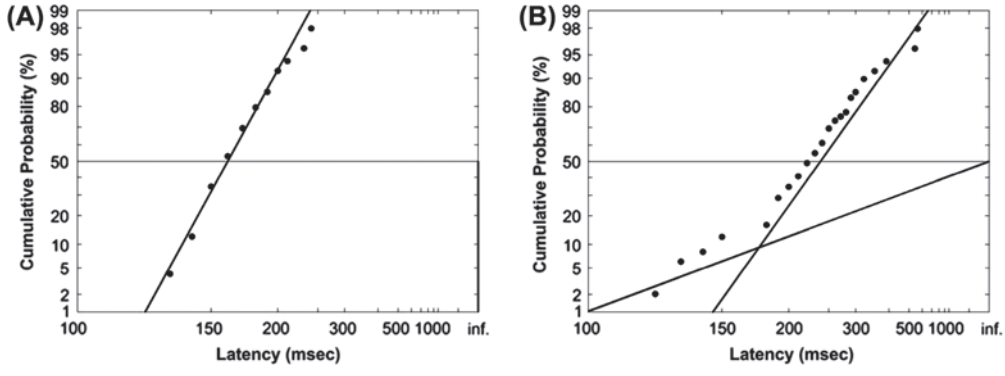

Figure 2. Representative reciprobit plots. A. Control subject: a single distribution of saccadic latencies conforms to one line of best fit on the reciprobit plot. B. Representative ALS patient: two distributions of saccadic latencies can be seen; the main distribution and a population of early saccades, which is characterized by a distinct line of best fit with a much shallower gradient.

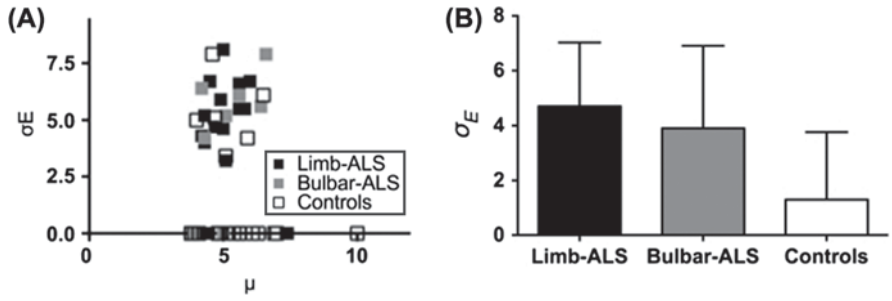

Figure 3. LATER parameters in ALS subgroups compared to controls. A. Both Limb ALS and Bulbar ALS subgroups had a significantly increased proportion of early saccades, indicated by an increased σ_E (Y-axis), compared to controls ($p<0.05$). The rate of decision-making, indicated by μ (X-axis), did not differ in either ALS sub-group compared to controls. B. Limb ALS and Bulbar ALS subgroups had a significant ($p<0.05$) increase in σ_E compared to controls, indicating an increased incidence of early saccades.

increased incidence of early saccades did not correlate with measures of motor or functional impairment, suggesting that saccadometry may provide an additional insight into extramotor features of ALS that are independent of the pattern or duration of pure motor involvement. In addition, the saccadometry findings of the present study were similar across Bulbar ALS and Limb ALS phenotypes.

Reports of saccadic eye movements in ALS have varied significantly, and a clear consensus has not yet emerged. Some studies have reported prolonged latency of voluntary saccades (4,26,27), reduced saccadic velocity (4,28), and poor performance on anti-saccade tasks (4,26,27). The inconsistencies in the literature may, to some extent, reflect that the protocols used have varied widely between investigators. For example, anti-saccade performance was normal in the present study, but abnormalities have been reported consistently in previous studies using different experimental paradigms (4,26,27). The anti-saccade protocol used in the present study measured 50 saccades, but by design only 25 were true anti-saccades. As such, a larger number of anti-saccades may have demonstrated impaired performance in the ALS group.

The present study specifically used the LATER model to enable a robust identification of an increase in early saccades, despite normal median saccadic latencies. There are several potential explanations for the apparent discordance between the findings of the present study and previous studies. For example, the mode of presentation and rate of progression of ALS are known to vary significantly from patient to patient (1), potentially making comparisons between study populations problematic. Furthermore, overt disturbances of eye movements may develop in advanced ALS, raising the possibility that saccadic abnormalities may be influenced by the stage of disease (29). Since the present study found no correlation between abnormalities of saccadic eye movements with traditional measures of motor impairment, disease progression, or symptom duration, the observed abnormalities may not simply be a function of advanced disease.

Previous studies have not specifically accounted for early saccades (4,26–28), which may have confounded the results. It is becoming apparent that it is not enough simply to report means of latency measures, even if accompanied by estimates of variability; certain features, potentially characteristic of pathological impairment, can only be seen when full distributions are measured and analysed, with an adequate number of trials in each data set (12,30). The ability to detect an increased proportion of early saccades independent from any effects on the main distribution is a significant advantage of the LATER model. In addition, previous studies have measured saccades under a variety of different circumstances, which may make the results difficult to compare with those of the present study. For example, some studies have measured latencies and velocities of remembered saccades (i.e. without an external target) (27,28) or anti-saccades (4,27) rather than reflexive saccades.

The neural correlate of early saccades is unknown, although a network of inter-connected cortical and sub-cortical structures may be involved (31). For example, one functional MRI study demonstrated activity of the inferior parietal lobe during reflexive saccades (32). Separately, changes in FEF activity have been demonstrated in normal primates during the gap experimental paradigm (as opposed to step paradigm used in the present study), in which early saccades are more common (33,34). In addition, activity of the dorsolateral prefrontal cortex in primates has been reported during the gap paradigm and during early saccades themselves (35). White matter tracts connecting the FEF, inferior parietal lobe, and the dorsolateral prefrontal cortex have been demonstrated recently (7).

Increased early saccades may reflect a specific pattern of pathology in ALS. Specifically, atrophy of the primary motor cortex and dorsolateral prefrontal cortex, which are in close proximity to the FEF (6), has been demonstrated in ALS (8). In addition, abnormalities of the anterior callosum, which may connect contralateral FEFs (7), have been demonstrated (8). Separately, an increased proportion of early saccades has been demonstrated in FTD and correlated with atrophy of the FEF (15). Importantly, frontal lobe atrophy has been demonstrated not only in FTD, but also in patients with combined

ALS and FTD, suggesting that anterior spread of pathology from the primary motor cortex may underlie abnormalities of saccadic eye movements in ALS patients. Consistent with this interpretation, functional magnetic resonance imaging studies have demonstrated FEF activity during visual fixation (36), which may be impaired in ALS (5).

The clinical significance of an increased proportion of early saccades in ALS is not currently known. Given the correlation between early saccades and rate of ALSFRS-R decline identified in the present study, early saccades may prove to be more frequent in patients with rapidly progressive disease. The relationship of early saccade frequency, and saccadic latencies, to traditional neuropsychological measures of cognitive performance should be explored, particularly as decision-making speed is fundamentally linked to saccadic performance. In particular, the relationship between saccadic eye movement abnormalities and executive function should be examined, since an increased incidence of early saccades has been identified in several contexts in which executive function would be expected to be impaired, such as frontal lobe lesions (37,38), concussion (39), and cognitive overload (14).

In summary, the present study has demonstrated subtle saccadic abnormalities in both Bulbar ALS and Limb ALS patient groups, with an increased proportion of early saccades despite normal median saccadic latencies of the main distribution. The significance of eye movement abnormalities in ALS remains uncertain. Saccadometry measures did not correlate with motor impairment, suggesting that investigation of saccadic eye movements may provide an additional insight into the clinicopathological spectrum of ALS.

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Supplementary material available online

Supplementary Figure 1 and Table I.