Frontal lobe dysfunction in amyotrophic lateral sclerosis

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Abstract

The aim of the present study was to investigate the involvement of frontal lobe dysfunction in amyotrophic lateral sclerosis (ALS) using ocular motor paradigms and neuropsychological testing. Fifty-one patients with ALS participated in the following ocular motor tasks: (1) a three-choice task and (2) a remembered saccade task. The patients underwent a clinical and neuropsychological evaluation. One-third of ALS patients presented with signs of frontal dysfunction, as determined by their high distractibility factors (DF) in the three-choice task and their performances in both the Wisconsin and Stroop tests. ALS patients exhibited longer latencies to eye movement than controls in the performance of the remembered saccade task, specifically in performance of both remembered and delayed saccades, but saccade accuracy was not impaired. Finally, performance indices of the ocular motor tasks, in particular the DF, was correlated only with the degree of dysarthria. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: ALS; Motor neuron; Frontal lobe; Anti-saccade; Remembered saccade; Working memory

1. Introduction

The clinical spectrum of ALS that was described last century by Charcot did not involve the ocular motor system. In fact, the degenerative process occurring in ALS affects mainly the corticospinal system and the anterior horn α-motoneurons while sparing the brainstem ocular motor circuitry, even in cases where the corticobulbar circuitry is also affected. Although earlier studies reported several slight oculographic abnormalities, including reduced saccadic eye movement velocity and low smooth eye pursuit gain [1–3] that were not apparent in the clinical evaluation of the patients, these findings have not been replicated in the recent literature [4,5]. Thus, it appears that the functional integrity of the saccadic system at the brainstem level is maintained. However, it is not known whether the ocular motor circuitry used in higher cognitive functions is affected by the disease.

Classically, cortical degeneration in ALS was believed to be restricted to the primary motor areas. However, several clinical, pathological, imaging and neuropsychological findings have challenged this overly simplistic notion [5–9]. A small minority of patients suffering from sporadic ALS presented with memory and cognitive dysfunction, indicating a dementia of frontal lobe type [9]. Furthermore, pathology studies as well as findings from PET, SPECT and MRI investigations have already revealed that the degenerative neuronal loss in ALS extends beyond the primary motor cortex and includes other areas, mainly in the prefrontal cortex [7–9]. In addition, evidence from neuropsychological studies supports frontal lobe involvement in sporadic ALS leading to significant impairment of executive functions. More specifically, ALS patients repeatedly demonstrate decreased performance in the Wisconsin Card Sorting Test, poor verbal fluency and difficulties in problem solving, as well as increased latencies when performing the random movement joystick test. However, they perform normally in visuospatial, naming and memory tests [10–13]. These findings are consistent with a frontal pattern of impairment rather than, for example, the tempo-parietal pattern found in Alzheimer’s disease.

The performance of a saccadic eye movement involves the activation of cortical areas and the pattern of cortical activation depends on the behavioral context in which the saccade is elicited. In the case of an anti-saccadic eye movement, the subject is instructed to perform an eye movement in the opposite direction of a visual target with...
respect to a central fixation point [14]. The suppression of the reflexive saccadic eye movement, or the “ocular grasping reflex” [15], toward the visual target is considered to require the intact functioning of frontal and prefrontal cortices. Patients with frontal lobe lesions have great difficulty in suppressing this reflex. The percentage of errors in the anti-saccade task, i.e. the eye movements toward the visual target, is called the distractibility factor (DF) and can be considered a quantitative measure reflecting impairment of frontal–prefrontal inhibitory functions. In schizophrenic patients, the DF in the anti-saccadic eye movement task is correlated with performance on specific neuropsychological tests of frontal lobe function, i.e. the Wisconsin Card Sorting Test [16].

Remembered saccades, or saccades to a previously displayed target in visual space, can be considered to reflect spatial working memory. Although the exact circuit for the execution of a remembered saccadic eye movement remains unclear, the participation of the frontal lobes and especially of Brodman area 46 is well established [17,18]. Several studies in animals have already revealed that the frontal lobes and especially dorsolateral prefrontal cortex (DLPFC) are involved in working memory function. In particular, during a delay response paradigm, neurons in these areas encode both the target location in space and the direction of the intended movement [19]. In addition, working memory performance is impaired when D1 antagonists are injected into the prefrontal cortex (PFC), further supporting the involvement of the PFC in working memory mechanisms [20]. Thus, it was deduced that the PFC and especially the DLPFC could be considered as a candidate location for specific working memory functions [20]. Given that similar cortical areas have been implicated in the performance of anti-saccadic and remembered saccadic eye movements, a question arises concerning the possibility of a dysfunction in both tasks in the case of frontal lobe impairment.

The study of Shaunak et al. [5] is the only one, to date, that focused on anti-saccades and remembered saccades in relation to ALS. ALS patients showed increased error rates and latencies in performance of both types of saccade. In contrast, performance of reflexive saccades and smooth pursuit was normal. Thus, the pattern of eye movement disorder in ALS is consistent with prefrontal dysfunction.

In this study, as in the study of Shaunak et al. [5], we evaluated the performance of ALS patients in the anti-saccade and the remembered saccade tasks. In addition, the patients performed an extensive battery of neuropsychological tests. Our aim was twofold: (1) to investigate correlations between frontal lobe dysfunction in ALS patients, as revealed by oculomotor system function, and the results from the neuropsychological testing; and (2) to investigate correlations of the oculomotor and neuropsychological data with clinical data to determine potential predictors of which nondemented ALS patients have concurrent cognitive impairment. Our study differs from the above mentioned in several important ways. First, we used a three-choice task instead of the classical anti-saccade task. The three-choice task imposes a greater attentional load, increases the degree of uncertainty of the forthcoming eye movement and forces the subject to perform more complicated visuomotor tasks (hence frontoparietal activation) for correct performance. Secondly, we quantified the neurological deficit via the Appel test and subsequently investigated correlations between Appel test parameters and oculomotor performance indices. Finally, the present study employed a larger number of subjects (51 vs. 17).

2. Materials and methods

2.1. Subjects

Fifty-one hospitalized ALS patients participated in the experiments. The control group consisted of 28 subjects. They were recruited from the patients’ spouses based on age and educational level. All spouses that were selected participated after giving their informed consent (Table 1). Patients and control subjects with an IQ score below 70 were excluded, as were patients and controls with depression (Beck’s inventory). The diagnosis of ALS was based on the criteria established by the World Federation of Neurology [22]. Quantitative evaluation for disability was calculated according to the Appel procedure [23]. An overview of the patient and control subjects data and related information is presented in Table 1.

2.2. Stimulation procedure and eye movement recording

Subjects were seated comfortably with the head immobilized by a headrest 120 cm in front of a gray monitor screen. The monitor displayed the visual targets used as stimuli. Horizontal (right eye) and vertical (left eye) eye movements were recorded using the infrared method (IRIS, SKALAR®). The infrared-oculographic (IROG) data as well as data concerning visual stimuli were sampled at 200 Hz and stored

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical characteristics of ALS patients and control subjects</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ALS patients (n = 51)</td>
</tr>
<tr>
<td></td>
<td>mean ± SD (min – max)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.8 ± 10.2 (36 – 74)</td>
</tr>
<tr>
<td>Male (number)</td>
<td>32</td>
</tr>
<tr>
<td>Female (number)</td>
<td>19</td>
</tr>
<tr>
<td>Education (years)</td>
<td>9.4 ± 4.2 (0 – 18)</td>
</tr>
<tr>
<td>Time since diagnosis (months)</td>
<td>25.5 ± 19.7 (6 – 84)</td>
</tr>
<tr>
<td>Appel score</td>
<td>69.2 ± 25.0 (30 – 123)</td>
</tr>
</tbody>
</table>

Eleven patients were diagnosed with the bulbar form of the disease whereas 40 were diagnosed with the distal form.
to the hard drive for further analysis. The experimental conditions are schematically depicted in Figs. 1 and 2.

2.2.1. The three-choice task

Subjects focused on a central fixation point (FP). A peripheral target (PT) appeared randomly to the left or to the right of the FP at a fixed eccentricity of 10°. The shape of the peripheral target varied randomly indicating to the subject the action to be taken: rectangle, saccade toward the target (pro-target saccade); triangle, continued fixation at the center (no move); circle, saccade in the opposite direction of the target (anti-target saccade). After a saccadic eye movement, the PT was extinguished, the FP was presented and a new trial was initiated when the subjects’ IROG indicated that eyes were fixated at the center (Fig. 1).

2.2.2. The remembered saccade task

Subjects focused on the FP. The PT appeared randomly to the left or to the right at 8° or 16°. In the remembered saccade task, the PT flashed for 200 ms, whereas in the delay task, it remained on. Subjects were instructed to wait for a randomized delay period of 2 to 5 s until the FP was turned off (go signal) to initiate action: a remembered saccade toward the location where the PT had previously appeared or a saccade toward the PT which was still on, respectively. In the remembered saccade condition, a corrective target was turned on at the remembered target location 1 s after the FP was turned off. Subjects were allowed to perform a corrective saccade, if necessary, and then fixate on the target until it was turned off (Fig. 2).

2.3. Analysis of eye movement data

For the three-choice task, we measured the mean latencies for all types of saccades (correct pro- and correct anti-saccades, error pro- and error anti-saccades), and calculated the DF. Error pro-saccades were defined as pro-target errors, i.e. inappropriate pro-saccades when an anti-saccade or no saccade was indicated. Error pro-saccades in both anti-saccade and no-move conditions were treated as one type of error and pooled together in all subsequent calculations. Error anti-saccades were defined as anti-target errors, i.e. inappropriate anti-saccades performed in the saccade condition. Latencies greater than 1000 ms or less than 80 ms (anticipatory saccades) were excluded from the analysis. The DF was defined as the percentage of errors (including both pro- and anti-saccade) and was calculated for each subject and across all subjects.

For the remembered saccade task, we calculated the mean latency for both remembered and delay saccades as well as the amplitude errors (dysmetria). The accuracy of remembered and delayed saccades was calculated using the formula: Accuracy = (expected amplitude – performed amplitude)/expected amplitude × 100 [17].

2.4. Neuropsychological evaluation

Patients and controls were screened extensively using a variety of neuropsychological tests. We present data from the performance in tests specific to frontal lobe function such as the Wisconsin Card Sorting Test (WCST) and the Stroop Test (Stroop). In addition, we present results for the Rey Complex Figure Recall (RCF), the Wechsler Adult Intelligence Scale (WAIS) and the Verbal IQ (VIQ). Performance IQ was not estimated in order to avoid bias due to the motor deficit of ALS patients. Subjects with a VIQ score of less than 70 were excluded from the study. In order to avoid the interference of depression, Beck’s depression inventory was administered and a cut-off point of 16 was used to exclude moderately and severely depressed subjects [24].

The following WCST parameters were scored: number of categories, perseverative and non-perseverative errors, total number of errors, perseverative responses, correct trials, percentage of perseverative errors and responses, and percentage of conceptual level of responses [25].

The Stroop was used to estimate the ability to suppress interfering information. We recorded the total number of correct responses during a constant period of time [26].
Finally, visual memory was assessed by the RCF 15 min after its presentation [27]. Patients with severe motor deficit were not given this test.

2.5. Statistical analysis

A normality test (Kolmogorov–Smirnov for one sample) was first performed for all variables under consideration. The Mann–Whitney U-test and the Students’ t-test were used as indicated for comparisons between patients and controls. Spearman rank order correlations were calculated for the correlations among the different variables. Chi-square and Fisher’s exact test were also performed. ANOVA, Pearson’s correlations (values of $R$ were calculated) and multiple regression analyses were performed after logarithmic transformation of data. Statistical analyses were performed using Statistica™ for Windows 95™ (1997).

3. Results

3.1. Clinical data

The clinical characteristics of ALS patients and controls are presented in Table 1. The majority of patients ($n=40$, 78%) presented with the distal form of the disease whereas the remainder ($n=11$, 22%) showed signs of bulbar onset. There were no significant differences between ALS patients and controls in terms of gender ($\chi^2=3.14$, $p>0.07$).
### 3.2. Eye movements

Tables 2A and 2B present measurements and statistical analyses regarding the ocular motor tasks.

#### 3.2.1. The three-choice task

**3.2.1.1. Latencies**. In the three-choice task, for both controls and ALS patients (Table 2A), the shortest latencies were observed for error pro-saccades whereas the longest were observed for error anti-saccades. Error pro-saccade latencies were significantly shorter than those in correct pro-saccades, which in turn were significantly shorter than correct anti-saccades. Latencies for error anti-saccades did not differ from those in correct anti-saccades for either controls or ALS patients. The comparison of latencies between the two subject groups showed shorter latencies of correct and error pro-saccades and error anti-saccades in the ALS patient group.

**3.2.1.2. Distractibility factor**. ALS patients exhibited a significantly higher average DF than the control group. In addition, more than 90% of their error saccades were protarget errors. Seventeen ALS patients (33%) had DF higher than the 99th percentile of DF values of the control group. The distributions of DF in ALS patients and controls are depicted in Figs. 3 and 4, respectively.

#### 3.2.2. The remembered saccade task

**3.2.2.1. Latencies**. Ocular motor data from the remembered saccade task are presented in Table 2B. There were no statistically significant differences between remembered and delay saccade latencies in either the control group or the ALS patient group. However, the ALS patient group latencies were significantly longer than those for the control group both for remembered and delay saccades.

**3.2.2.2. Dysmetria**. There were no differences in dysmetria between ALS patients and controls for either remembered or delay saccades. However, the remembered saccades were more dysmetric than the delay ones for both groups.

#### 3.2.3. Summary of the ocular motor results

In the three-choice anti-saccade task, the ALS group exhibited shorter latencies for correct pro-saccades, error pro-saccades, and error anti-saccades as well as higher DF compared to the control group. As for the remembered saccade task, although ALS patients had longer latencies in both remembered and delay conditions, their accuracy (as measured by dysmetria) was similar to that of control subjects.

### 3.3. Neuropsychological data

The results of the neuropsychological tests are given in Table 3. ALS patients differed from controls in 8 of the 11 categories of the WCST, whereas they did not differ in VIQ, Stroop and RCF scores.

### 3.4. Correlations

The results of correlation analyses between DF and, successively, clinical data, ocular motor data and neuropsychological test scores are presented in Table 4. We considered the DF to be the dependent variable indicative of frontal lobe dysfunction.
3.4.1. Correlations between DF and clinical data

A forward stepwise multiple regression was performed after the normalization of the demographic and clinical data. The following independent variables were used: age, education, time since diagnosis, and Appel score. The DF showed a statistically significant partial correlation with the Appel score, $R = 0.310$, $p = 0.04$ (DF $= -1.5 + 0.3 \times$ Appel score, $F$ to enter $= 3$) but was not correlated with age, educational level or time since diagnosis. In a second multiple regression, the Appel score was replaced by the subscores in the following measures: dysarthria (speech), swallowing, respiration, upper muscle strength, lower muscle strength. The DF was significantly correlated only with the speech score, $R = 0.38$, $p = 0.03$ (DF $= 25.3 + 0.36 \times$ speech score, $F$ to enter $= 3$).

3.4.2. Correlations between DF and ocular motor data (latencies and dysmetria)

The DF was significantly correlated with all the ocular motor parameters measured except the latency of delay saccades. The correlation coefficients (values of $R$) and the $p$ value for the $R$ between DF and each of the ocular motor parameters are presented in Table 4.

3.4.3. Correlations between DF and neuropsychological test results

We performed Spearman rank order correlations between the DF and each of the WCST, Stroop and RCF parameters. In the ALS patient group, DF was significantly correlated with 10 out of 14 test parameters. Specifically, significant correlations were found with the Stroop test and 9 of the 11

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**Table 3**

<table>
<thead>
<tr>
<th>Neuropsychological tests</th>
<th>Control subjects</th>
<th>ALS patients</th>
<th>Controls vs. ALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIQ</td>
<td>$103.12 \pm 10.56$</td>
<td>$97.96 \pm 13$</td>
<td>n.s. $(U=374, z=-1.09)$</td>
</tr>
<tr>
<td>Stroop</td>
<td>$78.7 \pm 23.2$</td>
<td>$63.15 \pm 25.7$</td>
<td>n.s. $(U=310, z=-2.49)$</td>
</tr>
<tr>
<td>RCF</td>
<td>$13 \pm 5.34$</td>
<td>$12.55 \pm 6.75$</td>
<td>n.s. $(U=244, z=-0.44)$</td>
</tr>
<tr>
<td>WCST Categories</td>
<td>$5.28 \pm 0.89$</td>
<td>$3.35 \pm 1.79$</td>
<td>$p&lt;0.01$ $(U=244, z=-0.46)$</td>
</tr>
<tr>
<td>WCST Trials</td>
<td>$111.57 \pm 15.9$</td>
<td>$117.8 \pm 20.2$</td>
<td>n.s. $(U=480, z=-1.83)$</td>
</tr>
<tr>
<td>WCST Correct resp.</td>
<td>$75.0 \pm 3.69$</td>
<td>$63.78 \pm 16.08$</td>
<td>$p&lt;0.01$ $(U=334, z=-3.45)$</td>
</tr>
<tr>
<td>WCST Errors</td>
<td>$36.57 \pm 15.38$</td>
<td>$53.97 \pm 22.36$</td>
<td>$p&lt;0.01$ $(U=354, z=-3.23)$</td>
</tr>
<tr>
<td>WCST Pers. resp.</td>
<td>$24 \pm 12.5$</td>
<td>$39.48 \pm 24.64$</td>
<td>$p&lt;0.01$ $(U=422, z=-2.47)$</td>
</tr>
<tr>
<td>Percentage pers. resp.</td>
<td>$20.14 \pm 8.68$</td>
<td>$31.58 \pm 19.61$</td>
<td>$p&lt;0.05$ $(U=446, z=-2.2)$</td>
</tr>
<tr>
<td>Percentage non-pers. resp.</td>
<td>$14.57 \pm 5.9$</td>
<td>$18.19 \pm 9.38$</td>
<td>n.s. $(U=480, z=-1.83)$</td>
</tr>
<tr>
<td>Percentage level resp.</td>
<td>$56.42 \pm 15.69$</td>
<td>$39.47 \pm 21.65$</td>
<td>$p&lt;0.01$ $(U=306, z=-3.76)$</td>
</tr>
<tr>
<td>Percentage of errors</td>
<td>$31.42 \pm 9.87$</td>
<td>$44.3 \pm 16.54$</td>
<td>$p&lt;0.01$ $(U=336, z=-3.43)$</td>
</tr>
<tr>
<td>Pers. errors</td>
<td>$21.57 \pm 10.18$</td>
<td>$34.87 \pm 20.57$</td>
<td>$p&lt;0.01$ $(U=412, z=-2.58)$</td>
</tr>
<tr>
<td>Percentage pers. errors</td>
<td>$18.28 \pm 7.02$</td>
<td>$28.41 \pm 17.61$</td>
<td>n.s. $(U=442, z=-2.25)$</td>
</tr>
</tbody>
</table>

Means and standard deviations are presented. The between group comparisons were conducted using the Mann–Whitney $U$-test. Resp. = responses, pers. = perseverative. Cells with statistically significant values of the $U$ statistic are marked in bold.

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Fig. 3. The distribution of DF in ALS patients. The $x$-axis represents DF values and $y$-axis the number of patients. The dotted line separates two distinct areas of accumulation of DF values.

Fig. 4. The distribution of DF in control subjects. Axes as in Fig. 3.
parameters of the WCST. DF was not correlated with performance of the trials and the non-perseverative responses of the WCST or with the VIQ and the RCF test scores.

We conducted a large number of separate correlations between DF and ocular motor and neuropsychological variables. While this increases the probability of type I error, the correlations follow the between groups comparisons, reinforcing these findings and the large number of significant correlations suggest that the majority have not occurred by chance.

4. Discussion

The main findings of our study may be summarized as follows. First, one-third of the ALS patients showed great difficulties when they had to suppress unwanted saccades, as reflected in the particularly high DF of this group. In addition, the ALS patient DF was correlated with abnormal scores in several categories of the WCST and with low performance in the Stroop test. These results suggest frontal lobe impairment in ALS patients. Second, ALS patients exhibited longer latencies than controls in both remembered and delay saccades without any difference in the accuracy of either saccade. No affect on remembered saccades suggests no deficit in the memorization of spatial information regarding the visual stimulus and thus no effect on spatial working memory as measured in this task. Third, the cognitive impairment was independent of many clinical parameters but significantly correlated with dysarthria as measured by the Appel test.

### 4.1. Anti-saccades in ALS

The performance of an anti-saccade [14] is a complex task since it demands the inhibition of the unwanted reflexive saccade. It involves the activation of posterior parietal cortical (PPC) areas for target localization and eye movement triggering [28] as well as the frontal motor areas (frontal eye field). In addition, it requires integrative function [29] of prefrontal areas.

In this study, ALS patients showed a high distractibility in the anti-saccadic eye movement task. The fact that the error saccadic eye movements were almost exclusive due to ineffective suppression of unwanted saccades toward the target, and that the errors were followed by correction, suggests that although the subjects understood the instruction, they could not avoid inhibit a saccade to the target when it appeared. Similar results have already been reported in a study on eye movements in ALS, although the experimental conditions differed slightly [5].

While the elevated DF seems to be related to a frontal lobe dysfunction, the precise localization of the suppression mechanisms in the frontal–prefrontal areas remains unclear [15,17,30,31]. The hypothesis of a frontal and/or prefrontal lesion in ALS revealed by the high DF in the anti-saccadic eye movement task is additionally supported by the results of neuropsychological testing. Specifically, the DF is statistically significantly correlated with the WCST results. A high correlation between errors in the anti-saccade task and WCST has also been found in schizophrenic patients and was considered a sign of frontal lobe dysfunction [16,52].
There was also a significant correlation between DF and low performance on the Stroop test, although there is no evidence of an impairment in the ALS patients on this test. In the present study, the latencies for both error anti-saccades (but not correct anti-saccades) and correct and error pro-saccades for the ALS patient group were shorter than those of the control subjects, whereas in the study of Shaunak et al. [5], these latencies were found to be longer than the control. The much more difficult three-choice paradigm we used requires longer overall processing time (inherently with greater variability) and may explain the discrepancy of our findings with that of Shaunak et al. [5].

Lesions of the human frontal lobes produce slight and usually transient ocular motor dysfunction. Aside from the well-established higher saccadic error rate, the effect of prefrontal lesions on saccade reaction time is still unclear. In the study of Guittot et al. [15], frontal patients exhibited latencies similar to those of control subjects, both for pro-saccades and anti-saccades. In addition, the study of Pierrot-Deseilligny et al. [17] failed to reveal any statistically significant difference of latencies among PFC, frontal eye field (FEF) and supplementary motor area (SMA) patients when comparing them to the control group. In contrast, the study of Braun et al. [33] showed a significant increase in express saccade latencies (in the range of 80–150 ms) when frontal patients performed a visually guided saccade in a gap ocular motor paradigm. Patients with small ischemic lesions affecting one FEF exhibited longer anti-saccade latencies when performing an overlap ocular motor task [34]. In a recent study of lesions affecting the FEF and/or the DLPFC, it was shown that FEF lesions were followed by an increase in the latency of short latency reflexive saccades [35]. These findings are contradictory and suggest that the FEF either plays a rather minor role in the preparation of saccades (as revealed by latency studies) [15,17], or contributes to the voluntary shiftings of attention [33] and underlines the volitional characteristics of a saccadic eye movement. Nevertheless, the results of our study and one of the above mentioned [35] allow us to assume that the shorter latencies of reflexive saccades may be attributed to an inactivation of the FEF-collicular inhibitory pathway. We might hypothesize that, in frontal patients, the signal for saccadic eye movement onset bypasses the FEF and reaches the disinhibited colliculi directly. In other words, the slow voluntary controlled system is substituted by the fast reflexive one for triggering an eye movement and this “hyperactive visual grasp reflex” can be attributed to the frontal lobe impairment.

4.2. Remembered saccades in ALS

The frontal lobes are involved in the performance of memory-guided or remembered saccades. Studies with regional cerebral blood flow during a remembered saccade task showed an activation of several areas such as the FEF, SMA, DLPFC and PPC [35,36]. In the present study, ALS patients presented a slight but significant increase in remembered and delay saccade latencies similar to that reported previously under slightly different experimental conditions [5]. Lesions at several sites including the frontal, prefrontal and parietal cortices can affect remembered saccade latency [17]. The possibility of frontal involvement is supported by neuropsychological test results, but the possibility of parietal impairment cannot be excluded. Some evidence for parietal cortical involvement in ALS comes from PET studies [37] and frontal (dorsolateral prefrontal) and parietal lesions, showing an increase in both the latency of saccades and the degree of dysmetria [17]. Several findings implicate the DLPFC as the candidate location for working memory dysfunction [21].

4.3. Cognitive deficits and clinical correlates

The association of motor neuron disease with cognitive dysfunction has been described [6,38,39]. In our study, frontal lobe dysfunction was found in 30% of a large number of patients screened with WCST, Stroop, RCF and WAIS-VIQ. The present study is in agreement with one of the previous studies [39] in that one-third of our non-demented patients showed suppression difficulties indicating frontal lobe deficit.

More interestingly, the DF was correlated with only one subcategory of the Appel score, namely dysarthria. In spite of the purely clinical rating of speech and deglutition in the Appel procedure, which might be inappropriate for precise detection of bulbar symptoms, the selective correlation of dysarthria with frontal dysfunction is interesting in the light of recent findings. In particular, the presence of pseudobulbar palsy in ALS is associated with frontal lobe impairment [10]. It has recently been suggested that cognitive impairment and dysarthria could be considered as a single underlying process based on the absence of the calcium-binding proteins [40,41].

Our findings shows that a subgroup of ALS patients present clear and subclinical frontal deficits. The question remains as to whether the ALS subgroup shares a common pathology with the rest of the ALS patients reflecting a unique disease with quantitatively different expression, or whether the ALS population could be divided in two distinct and qualitatively different diseases according to the presence or absence of the frontal deficit. Several studies have proposed that the phenotypic expression of ALS varies between different forms. Thus, the disease has been described as sporadic without cognitive impairment, sporadic with cognitive deficits and coexistent ALS with frontal dementia [9,10,42], raising the question of whether the clinical spectrum of ALS is a continuum or discrete entities.

In conclusion, it seems that ALS is a disease that affects higher cognitive frontal functions such as suppression of unwanted saccadic responses and preparation of remembered saccades.
References