J Neurol (2008) 255:532–538
DOI 10.1007/s00415-008-0734-9

ORIGINAL COMMUNICATION

# Signs of impaired selective attention in patients with amyotrophic lateral sclerosis

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Received: 23 February 2007
Received in revised form: 24 July 2007
Accepted: 3 September 2007
Published online: 18 February 2008

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**Abstract** The evidence for involvement of extramotor cortical areas in non-demented patients with amyotrophic lateral sclerosis (ALS) has been provided by recent neuropsychological and functional brain imaging studies. The aim of this study was to investigate possible alterations in selective attention, as an important constituent part of frontal brain function in ALS patients. A classical dichotic listening task paradigm was employed to assess event-related EEG potential (ERPs) indicators of selective attention as well as preattentive processing of mismatch, without interference by motor impairment.

A total of 20 patients with sporadic ALS according to the revised El Escorial criteria and 20 healthy controls were studied. Additionally a neuropsychological test battery of frontotemporal functions was applied.

Compared with the controls, the ALS patients showed a distinct decrease of the fronto-precentral negative difference wave (Nd), i.e., the main ERP indicator of selective attention. Analysis of the P3 component of the ERPs indicated an increased processing of non-relevant stimuli in ALS patients confirming a reduced focus of attention. We conclude impaired selective attention reflects a subtle variant of frontotemporal dementia frequently observed in ALS patients at a relatively early stage of the disease.

**Key words** ALS · event related EEG potentials · neurophysiology · frontal brain function

## Introduction

Apart from the progressive degeneration of upper and lower motoneurons as the clinical hallmark of amyotrophic lateral sclerosis (ALS), there is increasing evidence for structural alterations and functional deficits outside the primary motor areas [1, 2, 11, 12, 27, 37]. Neuropsychological data [1, 2, 20, 34] and functional imaging investigations [11, 12, 17, 19, 37] point to an integral prefrontal and fronto-temporal dysfunction in sporadic ALS. The question is which behavioral consequences this may have in non-demented ALS patients.

We know that the prefrontal cortex plays a crucial role in generating higher brain functions like planning, concept formation and attention regulation. Within the domain of attentional regulation particularly selective attention is linked to the executive control of the prefrontal lobe [14–16, 29]. This study therefore examined whether this specific aspect of prefrontal lobe function is altered in ALS patients in comparison to healthy controls.

We used endogenous event-related potential (ERPs) measures that enable to assess different aspects of attention without interference by motor action. ERP components of special interest in this context are the "nega-

JON 2734

tive difference" (Nd) wave reflecting the focus of attention [22, 26], the N1 as a nonspecific arousal response and the mismatch negativity (MMN) that is related to the preattentive processing of unattended stimuli. Finally, the P3 is a late positive ERP component related to the cognitive processing of task-relevant input.

## Methods

### Patients and controls

Twenty non-demented ALS patients (14 male, 6 female) diagnosed according to the revised El Escorial Criteria [4] were examined. Mean (SD) age was 58.5 years (11.5) ranging between 31 and 75 years. Mean disease duration (SD) was 18.4 months (12.3) ranging from 5 to 49. The clinical history revealed a spinal onset of ALS symptoms in 16 patients and a bulbar onset in four. Besides a status examination, clinical evaluation included the following scales: "ALS severity scale" [9], "ALS score" [5] and the "modified Norris Neuroscale" [4]. All patients were taking riluzole.

Twenty age-matched subjects without any history of brain damage, neurological or psychiatric disease served as control group (CG). Mean (SD) age of the controls was 57.6 years (10.8) which was well comparable with that in the patients. None of the patients or controls was taking any medication that was likely to affect vigilance or mental capabilities. All patients and controls were right-handed. All subjects gave their informed consent to participate in the study.

In both patients and the controls the Multiple Word Discrimination Test form B (MWT-B) [18] and Beck's depression inventory (BDI) [8] were assessed to screen for premorbid intelligence and emotional well-being and their influences on ERP and neuropsychological tests. Due to high scores in some questions of the BDI that interfere directly with the patients' disability related to ALS, this information from 4 patients was not interpreted as an expression of depression. There was no statistically significant difference in the ND of these patients with BDI values higher than 18 in comparison to the patients with low BDI values (Fz: $p = 0.54$; Cz: $p = 0.41$).

There was no evidence of clinically relevant depression or basic intellectual decline in the patient group (PG). A summary of subjects' characteristics is presented in Table 1.

**Table 1** Demographic, behavioural and clinical characteristics of experimental groups

| | ALS patients (N = 20) | Controls (N = 20) |
|---|---|---|
| Male/female ratio (patients vs controls) | 14/6 | 13/7 |
| Age, in years | 58.5 ± 11.5 | 57.6 ± 10.8 |
| Duration of disease (in months) | 25.5 ± 21.4 | na |
| MWT-B (items) | 27.2 ± 4.7 | 34.1 ± 2.6 |
| Beck Depression Inventory | 12.7 ± 6.3 | 5.9 ± 3.5 |
| Norris Neuroscale, modif.% | 74.5 ± 23.1 | na |
| ALS severity scale | 25.5 ± 10.6 | na |
| ALS Score Caroscio A | 1.9 ± 0.9 | na |
| ALS Score Caroscio B | 3.4 ± 1.2 | na |
| ALS Score Caroscio C | 1.8 ± 0.9 | na |

*MWT-B items* number of correct solutions; *BDI* score 11–17, mild depressiveness; *BDI > 18*, clinically relevant depression; *Norris* modif.%; *na* not applicable. Means ± SD are indicated where appropriate

### Stimuli and procedure

A dichotic listening paradigm including the two-dimensional (location, pitch) discrimination of acoustic stimuli according to Hillyard et al. [10] was used to assess ERPs. Programming and stimulus presentation were executed with the "STIM" software package of Neuroscan (Sterling, Virginia, USA). During the session, a total of four blocks consisting of 400 tones each was consecutively presented to the subjects via earphones. The stimulus sequence of each block consisted of two combinations of a standard and a deviant tone respectively differing in frequency and in pitch (combination one: frequent (20 % probable) standard tone 800 Hz, infrequent (80 % probable) deviant tone 840 Hz; combination two: frequent (20 %) standard tone 1200 Hz, infrequent (80 %) deviant tone 1260 Hz). Thus each block included four types of tone peeps. They were randomly produced by a tone generator and presented in the way that each ear received only one of the above mentioned combinations. Simultaneous occurrence of a tone in both ears was excluded. The interstimulus-interval was randomized between 0.8 to 1.4 s.

Subjects were instructed to focus attention on one ear during a block and to count the infrequent deviant tones (targets) in this ear. Within this selective attention instruction, four qualities of input could be categorized: (1) attended, but not task-relevant standards and (2) attended, task-relevant (counting) deviants ("targets"); (3) unattended standard and (4) unattended deviant tones.

### Data acquisition and processing

For EEG recordings, electrodes (Ag/AgCl) were attached at F3, Fz, F4, C3, Cz, C4, P3, Pz, P4 according to the 10–20 System. For artifact recognition, two additional electrodes measuring vertical and horizontal eye movements were placed. Data acquisition was performed by the "Scan" software (Neuroscan, Sterling, Virginia, USA). 2000 ms epochs were selected offline spanning intervals from 400 ms pre-stimulus onset to 1600 ms post-stimulus onset. Data were screened using automated algorithms and visual inspection to remove epochs with eye blinks and other artifacts.

ERP were averaged separately for the four types of tones. From these ERPs the following components were extracted.

(1) The N1 component (80–150 ms post-stimulus) as a correlate of a global cortical arousal response.
(2) The Nd (180–360 ms) as a correlate of selective attention.
(3) The MMN (180–360 ms), considered to reflect automatic processing of stimulus mismatch.
(4) The P3 (300–700 ms) considered to be a correlate of late cognitive processing. A supplementary analysis was performed on P3 components evoked to the deviants in the unattended ear.

### Neuropsychological assessment

The neuropsychological test battery was designed to provide behavioural data complementary to ERPs by assessing prefrontal lobe functions associated with executive and attentional control.

#### Executive functions

Coping with perceptual interference was assessed by a modified version of Stroop's Colour Word Interference Test (CWIT) [36] adapted by Bäumler [3]. In three subtests, a verbal (colour words; CWIT1), non-verbal (colour dots; CWIT2) and mismatch condition (colour words; CWIT3) were presented. Assessment parameters were: reading time (colour words), naming time (colour dots), interference time (colour words) and error rate. Verbal fluency was assessed by a modified Controlled Word Association Test (COWAT) [38]. Naming and/or writing of words beginning with the letters "F-A-S" indexing semantic (formal-lexical) fluency (COWAT1) and naming of animals indexing categorical fluency (COWAT2) was required. Assessment pa-

rameter was the number of words generated within a defined time-period in the respective condition. Response time included a span of 1 minute in order to reduce bias by mechanical slowing of speech or writing. As verbal fluency impairments in ALS patients are not caused or exaggerated by an impairment in phonological loop functions or in primary linguistic abilities [2], the test modality (oral or written) was chosen with respect to the patient's clinical deficits. All controls were tested in the written modality. Figural (design) fluency was assessed by the non-verbal 5-Point Fluency Test (5-PFT) [32]. It requires the generation of as many unique geometrical designs as possible by interconnecting five dots within a time period of 3 min. Assessment parameters were the number of unique designs and repetitions.

#### Attention control

Selective attention as the ability to focus attention to matching input and gating irrelevant input was assessed by the "incompatibility" task paradigm ($TAP_{(inc)}$) from the TAP attention battery [41]. Within this task stimulus-response compatibility effects were tested; therefore arrows were presented for 0.1 s at an angle of 2.7° from midline pointing to the right or the left side bilateral to a fixation point. Depending on the arrow's direction the response had to be given pressing a pusher in the right or left hand. The task required the patient's reaction to compatible stimulus-reaction settings (direction of the arrow and field of view are the same, e.g. arrow pointing rightwards within the right field of view) embedded among incompatible settings presented with visual cues. Assessment parameters were reaction time (RT), number of correct and false reactions.

### Statistical analysis

Statistical analysis of ERP data was done by analysis of variance (ANOVA) with Group (ALS versus control) and Topography (electrode position) as repeated measures factors. The level of significance was considered 0.05.

Statistical analysis of neuropsychological data was performed using t-test.

## Results

### Event related potentials

#### N1 component

Distinct N1 components of the ERPs were elicited by both attended and unattended stimuli with a predominance over the fronto-precentral midline (Fz and Cz) in both groups. Statistical analysis did not reveal any significant difference between groups for the N1 peak amplitude and latency. N1 after attended stimuli did not differ from N1 after unattended stimuli and this again held for both groups.

### Negative difference wave – Nd:

A marked Nd (mean, ± SD) at Fz (–0.76 mV, ± 0.99) and Cz (–0.96 mV, ± 1.09) was revealed in the controls, whereas in the patient group there was nearly no discernible Nd at these leads (Fz: –0.26 mV, ± 0.70; Cz: –0.20 mV, ± 0.86). Statistical analysis confirmed a highly significant decrease in Nd in the ALS patients for the fronto-central midline (Fz and Cz: $f = 4.91$, $p = 0.032$) and across all medial and lateral frontal and central leads (F3, Fz, F4, C3, Cz, C4: $f = 8.19$, $P = 0.006$). Inspection of waveforms from individual patients and controls revealed that Nd was completely lacking in a considerable number of ALS patients, contrasting with Nds of substantial size in their healthy controls. Thus, 19 out of 20 controls but only 7 out of 20 patients generated a prominent Nd. The reason is indicated in Fig. 1a and b showing that attended as well as unattended stimuli elicit small negative shifts of similar size in the patients, whereas in the controls attended input is associated with a distinctly higher negative potential shift. The decrease of the ND did not correlate with the severity of the disease.

#### Mismatch negativity (MMN)

Both groups generated a marked MMN indicating differential processing of deviant tones in the unattended ear as compared with the unattended standards. Mean MMN amplitude predominated over the frontal-precentral midline and averaged (mean, SD) –1.31 mV (0.88) at Fz and –1.70 mV (1.24) at Cz in the patients as compared to –1.32 mV (1.32) at FZ and –1.47 mV (2.32) at Cz in the controls. There was no significant difference between groups at these sites ($p = 0.80$).

#### P3 component

As expected, distinct P3s were generated to task-relevant deviant stimuli (targets) in the attended ear with a clear predominance over the parietal convexity. P3s were nearly identical in patients and controls with respect to amplitude measures (Fig. 2a).

P3 peak amplitude at Pz averaged 7.31 mV (5.41) in the patient group and 7.33 mV (3.85) in the controls ($f = 2.0$, $p = 0.16$; $f = 0.82$, $p = 0.37$, for area under curve.

Analysis of ERPs to the stimuli of the unattended ear revealed that unattended deviant stimuli evoked a more pronounced P3, particularly in the early phase, in the patients than in the controls (Fig. 2b). A higher P3 peak amplitude, a vaster P3 area under curve and a shorter P3 latency could be delineated. P3 peak amplitude averaged 4.78 mV (3.50) in controls but only 4.06 mV (2.33) in patients ($f = 7.108$, $P = 0.011$).

### Neuropsychological assessment

The results of the neuropsychological tests pointed to deficits in frontal brain related functions within the patient group; the results are summarized in Table 2.

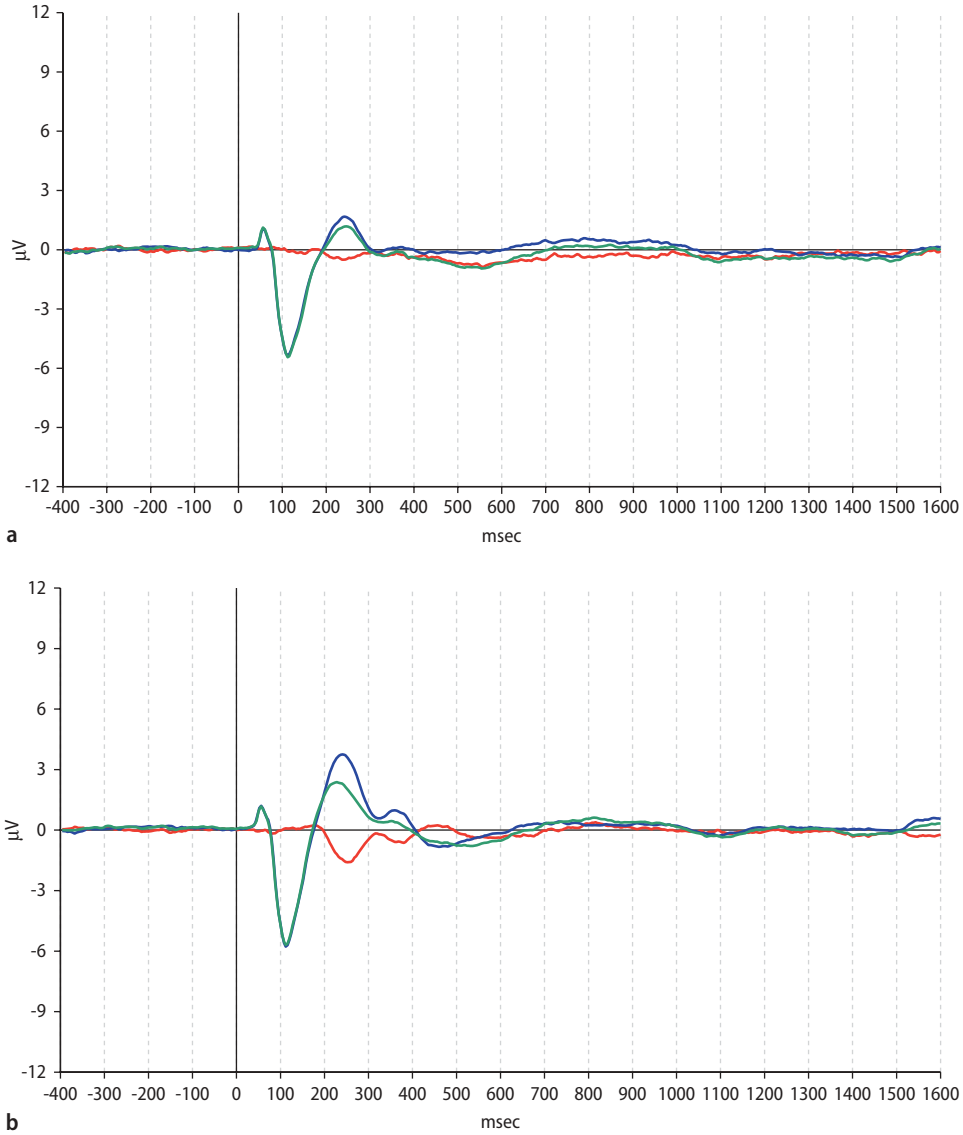


**Fig. 1** Nd wave (red) and ERPs to attended (green) and unattended (blue) standard tones recorded from Fz in the ALS patients (n = 20) (**a**) and in healthy controls (**b**) Positive is upward

## Discussion

The primary finding of the present study is that ERPs associated with selective attention are markedly altered in a group of ALS patients as compared to healthy controls matched for age and gender. As Vieregge et al. [39] have shown this is reflected by distinct reductions of the negative difference (Nd) wave over the frontal-precentral cortex. Our data elicit that this finding is not merely a group effect but can be traced to the single patients. Because Nd reflects a difference in ERP activity to attended relative to unattended sensory input, a reduced Nd implies a proportionally weaker focus of attention to the relevant stimuli in ALS patients. Additionally our P3 data indicate that differences between ALS patients and controls manifest themselves also in later stages of processing once a stimulus has been selected. P3 is considered a sign of further task-related processing of input recognized as relevant that eventually leads to an updating of current working memory content [7, 40]. But the difference did not pertain to the classical P3 elicited by the attended task-relevant stimuli (targets) which revealed to be absolutely comparable between patients and controls. Instead, ALS patients displayed an increased and earlier P3 to the rare tones in the unattended ear suggesting increased cognitive processing of irrelevant stimuli. Since it was especially the earlier P3 portion that constituted the group difference the difference might pertain particularly the P3a known to process information not relevant for task performance [35]. We conclude that the increase in P3 to unattended rare tones in ALS reflects a consequence of impaired selective attention in these patients.

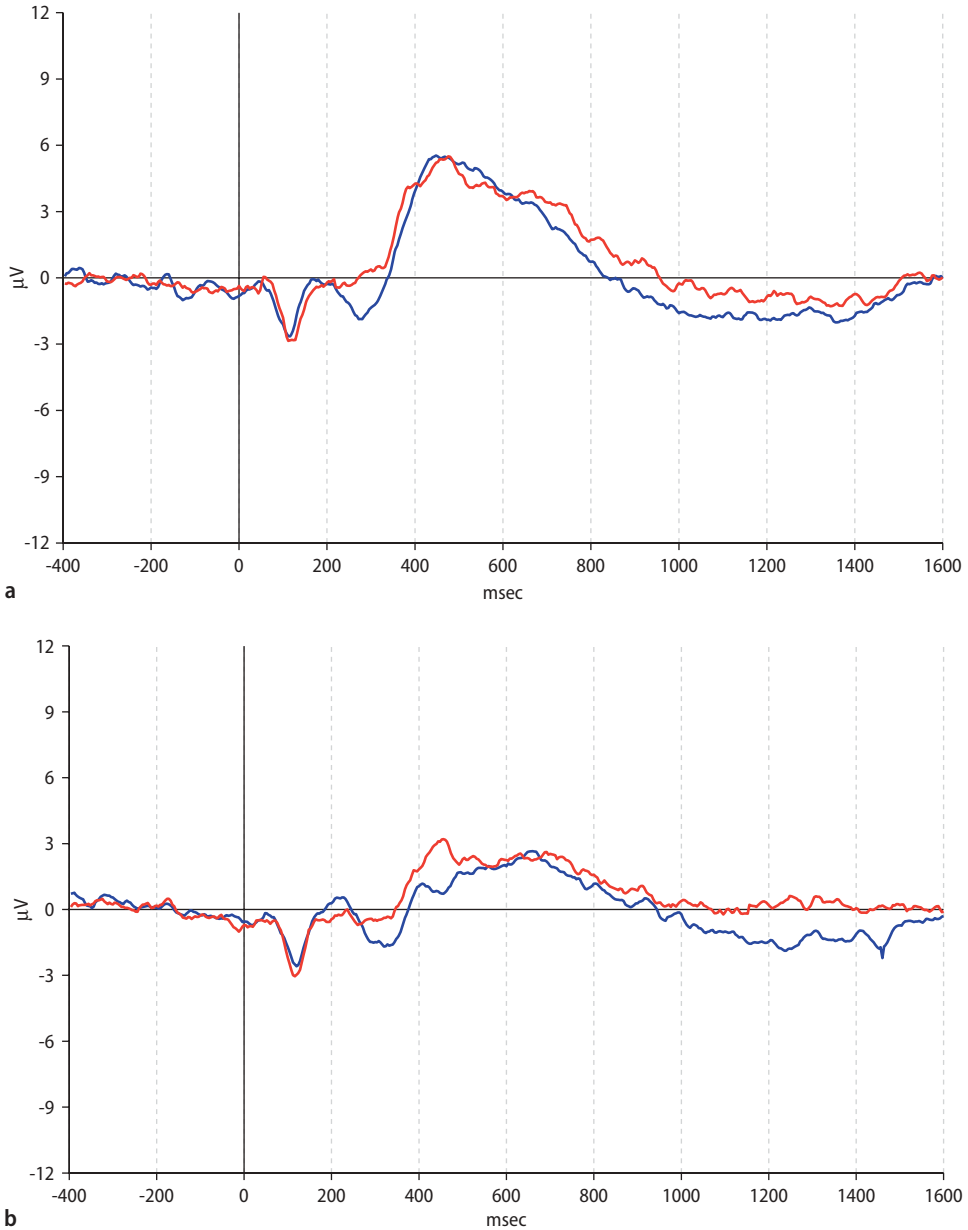


**Fig. 2** P3 to rare deviant tones in the attended channel (**a**) and in the unattended channel (**b**) in ALS patients (red, n = 20) and healthy controls (blue, n = 20) recorded from Fz. Positive is upward

**Table 2** Results of the neuropsychological tests

| Neuropsychological Test | Patients | Controls | Level of significance |
|---|---|---|---|
| CWIT1 (reading time) | 37.6 (5.27) s | 36.2 (7.69) s | $p > 0.05$ |
| CWIT2 (naming time) | 50.9 (7.22) s | 54.2 (10.55) s | $p > 0.05$ |
| CWIT3 (colour-word interference) | 95 (26.87) s | 98 (30.67) s | $p > 0.05$ |
| COWAT1 (number of words) | 22.5 (6.7) | 33.5 (8.1) | $p < 0.001$ |
| COWAT2 (number of words) | 13.2 (5.1) | 15.4 (3.0) | $p > 0.05$ |
| 5-PFT | 17.7 (8.3) | 28.2 (5.4) | $p < 0.01$ |
| $TAP_{(inc)}$ subtest incompatibility | 568.7 ms (106.7) | 609.6 ms (120.1) | $p < 0.03$ |

CWIT Means ± SD; *CWIT* colour word interference test; *COWAT1* formal lexical fluency; *COWAT2* categorical fluency; *5-PFT* nonverbal fluency, number of generated unique designs

Referring to the Nd and P3 findings it can be suggested that ALS patients allocated roughly the same processing resources to both attended and unattended stimuli thereby minimizing Nd and increasing the P3 in the unattended ear. Thus impaired selective attention appears to be the consequence of inadequately high processing of irrelevant sensory input in our ALS patients.

Interestingly, the N1 of the ERPs was not changed in the ALS patients; N1 reflects primarily non-specific cortical arousal to stimulus input [25]. However depending on the stimulus parameters, N1 may overlap with Nd related activity in a dichotic listening paradigm [21, 24]. In a dichotic listening situation, Vieregge et al. [39] found deficits in ALS already to begin with the N1 selection process which appears to diverge from the present observations. However, the reason for this difference is likely the modified paradigm in that study where the difference in pitch between attended and unattended stimuli was greater and also these stimuli differed in duration. In this way discrimination of attended and unattended stimuli may have been easier leading to an earlier onset of Nd that in turn overlapped preceding N1. The notion of unchanged preattentive stimulus processing in ALS patients is further supported by our finding that MMN was closely comparable in both groups. MMN is regarded as a specific processing correlate of deviant stimuli that takes place primarily within primary and secondary auditory cortical areas independent of the focus of attention regulated via frontocortical circuitry [23]. In combination, unchanged N1 and MMN in the ALS patients suggest that automated types of stimulus processing are left unchanged by the disease process, at least during the earlier stages studied here.

The functional interpretation of the described ERP alterations adds credit to the notion that prefrontal lobe functions are specifically affected by ALS pathology, i.e., in non-demented patients. Supporting evidence comes from functional imaging studies showing that selective attention is linked to the executive control of the frontal lobes [6, 30, 31, 33]. The interpretation is also supported by our neuropsychological findings indicating deficits in verbal and non-verbal fluency and certain aspects of the incompatibility subtest of the TAP attention battery, all crucially associated with frontal lobe functioning [1, 2]. Moreover, the attentional dysfunctions seem to occur early in the disease course since we examined our ALS patients in initial to medium stages. Neuropsychological deficits have also been found to appear early in the course of ALS, and not in parallel with motor decline [1, 2, 34]. From this most compelling evidence we conclude that impaired selective attention is part of an extended spectrum of ALS symptoms and that it is frequently observed in non-demented ALS patients at a relatively early stage of the disease. Maybe it reflects a subtle variant of fronto-temporal dementia (FTD) known to affect a smaller portion of patients.

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