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Research report

Cognitive impairment in amyotrophic lateral sclerosis: evidence from neuropsychological investigation and event-related potentials

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Abstract

The presence of subclinical cognitive impairment in patients with amyotrophic lateral sclerosis (ALS) is investigated using neuropsychological assessment and event-related potential recordings (ERP). An extensive battery of neuropsychological tests assessing the domains of attention, memory, language, visuo-spatial and executive functions were administered to 20 non-demented patients with sporadic ALS and 13 age- and education-matched healthy control subjects. Mismatch negativity (MMN), P3b, P3a (novelty P300) and contingent negative variation (CNV) were recorded. ALS patients were significantly impaired in tests of working memory, sustained attention, response inhibition, naming, verbal fluency and complex visuo-spatial processing. The memory impairment seemed to be secondary to deficits in forming learning strategies and retrieval. In ERP recordings, P3a and P3b amplitudes of ALS patients were lower compared with the controls, P3a latencies were significantly longer and mean CNV amplitudes were higher. These results indicate subclinical impairment of cognitive functions in patients with ALS. The pattern of cognitive impairment suggests the dysfunction of the frontal network.

Theme: Disorders of the nervous system

Topic: Degenerative disease: other

Keywords: Amyotrophic lateral sclerosis; Neuropsychology; Event-related potential; Frontal dysfunction

1. Introduction

Neuropathological [50,55], neuropsychological [2,4,5,19,26,27,43], neuroimaging [1,3,6,26,34,36,38, 39,41,42,73] and electrophysiological [28,47–49,72] studies provide evidence for extra-motor involvement in non-demented patients with amyotrophic lateral sclerosis (ALS). Dementia may be observed in 3.5% of sporadic ALS patients [37], where the clinical profile of dementia is of frontal network type [37,45,53,70]. Milder cognitive dysfunction is significantly more common in non-demented ALS patients and is reported to be as high as 35% in a study with a large number of subjects [43]. In previous reports, impairment in verbal reasoning, category formation, visual attention and picture sequencing were the most consistent findings. Memory and learning were found to be impaired in tasks such as prose and picture recall, word list learning and recall and paired associate learning [2,4,5,19,26,27,43]. Functional and structural imaging studies suggest frontal involvement in non-demented ALS patients [3,6,34,36,41,42].

Event-related potentials (ERP) have been widely used to assess electrophysiological correlates of cognitive deficits in various clinical populations [57]. Studies on demented patients revealed prolonged P300 latencies [58]. ERP recordings in non-demented patients with sporadic ALS also showed prolonged N200 and P300 latencies compared to healthy controls [28]. Münte et al. reported ERP patterns

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that indicate abnormal memory processing in ALS patients [47]. Recently, Vieregge et al. showed that processing negativity (PN), a negative shift of the ERP evoked by attended tones in relation to unattended tones, was smaller in frontal and central leads of ALS patients than in age-matched healthy control subjects. The authors found that the reduction in the amplitude of PN correlated with functional motor impairment [72].

The aim of this study is to investigate the presence and pattern of cognitive dysfunction in early, relatively less handicapped and non-demented ALS patients using a comprehensive neuropsychological battery and a set of ERP paradigms. These include oddball paradigm (P3b), the mismatch negativity (MMN), and especially novelty-P300 (P3a) and CNV paradigms, both of which are closely related with the activity of frontal areas.

2. Materials and methods

Twenty patients with probable or definite sporadic ALS according to the El-Escorial criteria [16] were recruited. Fifteen patients were male. All patients were evaluated by two neurologists (HAH, HAI) and they all had clinical and electrophysiological proof of both upper and lower motor neuron involvement. None of the patients had a history of cognitive, behavioral symptoms, mood disorders or systemic diseases. They were not on psychoactive drugs or any other medication (riluzole was not approved for clinical use in Turkey during this study) that could alter cortical excitability. All patients had motor symptoms for at least 3 months and all were older than 35 years of age. Patients had at least 5 years of education and were free of severe verbal or motor disability that would interfere with neuropsychological testing. The mean age was 53±11 years and mean duration of formal education was 8.7±3.7 years. The mean duration of illness was 18.3± 12.4 months (range: 3–24) and the mean score on the ALS functional rating scale was 33±2.5 (range: 29–36) [9]. All patients had spinal onset; four patients with bulbar findings had mild articulation difficulties. The control group consisted of 13 healthy volunteers (10 male, 3 female) within the same range of age and education. The mean age was 52±12 years and the mean duration of education was 9.7±4.4 years. All patients gave informed consent and the study was approved by the ethics committee of Istanbul Medical School.

Dementia or major depression were excluded by clinical interview and by screening cognitive and affective domains using the Mini Mental Status Examination (MMSE) [25] and Hamilton depression scale (HDRS) [30], respectively.

After the initial assessment to ascertain diagnosis and compliance with study inclusion criteria, a battery of neuropsychological tests was administered, and the electrophysiological recordings were performed in a different session.

Table 1
Neuropsychological test battery

Neuropsychological tests
WAIS-R, digit span subtest (DS) [74]
Continuous performance test (computerized) (CPT) [32]
Verbal fluency (F-A-S test and category naming) [46,67]
Trail making test (Trails A and B) (TMT—A and B) [68]
Delayed recognition test (computerized) (DRT) [7]
Serial digit learning test (SDLT) [12]
Stroop test [66]
Go–no-go test (computerized-auditory stimuli) [63]
Boston naming test (30-item Turkish modification) (BNT) [33]
California verbal learning test (CVLT) [20]
Benton's line orientation (BLO) [14]
Benton's facial recognition (BFR) [13]
WAIS-R, block design subtest (BD) [75]

2.1. Neuropsychological testing

A comprehensive neuropsychological test battery was used to test different domains of cognition, with an emphasis on executive functions. The battery is shown in Table 1 and the classification of tests for various cognitive domains are shown in Table 2.

Table 2
The classification of the neuropsychological tests—classified under cognitive domains

Neuropsychological tests according to cognitive domains
Attention
DS-forward and DS-backward (DS-fwd, DS-bwd)
CPT-total correct responses
Executive functions
Working Memory
SDLT
DRT
Resistance to interference
CPT-commissions
Go–No-Go commissions
Stroop-interference
Perseverance
Verbal fluency
Set shifting
TMT-B
Language
BNT
Memory
CVLT
Visuo-spatial processing
BFR
BLO
BD

2.2. Event-related potentials

ERP recordings included P300 in a classical auditory oddball paradigm (P3b) [57], auditory P3a in a novelty paradigm [18,35,40], CNV [15,59] and MMN [24].

Subjects were seated on a comfortable chair with a headrest in an electromagnetically isolated, sound-attenuating room and allowed to relax. During recordings, subjects were instructed to minimize blinking and to fixate a marker on the wall to reduce eye movements as much as possible. Because a large set of ERP experiments were carried out on each subject, this instruction was necessary to obtain a sufficient number of clean trials in each experiment, although there are studies reporting that such instructions might reduce the N1 and P300 amplitudes [54,71]. As both patient and control groups were instructed in the same way, the possible effects of this instruction should not affect the comparative results.

The mismatch negativity (MMN), P3b, P3a and contingent negative variation (CNV) were measured using the following four experimental paradigms:

(1) Mismatch (passive oddball) paradigm: Two types of tone bursts of 70 dB intensity and 50 ms duration with 10 ms rise and fall times were presented binaurally through earphones at a rate of a tone every second. Deviant stimuli were 2000 Hz tones and were interspersed pseudo-randomly among the standard tones of 1000 Hz with a probability of 0.2. The subjects were asked to read a newspaper article they found interesting. A total number of 150 trials with 120 standard and 30 deviant stimuli were recorded.

(2) Active oddball paradigm: Non-targets were 1000 Hz and targets were 2000 Hz tone bursts of 70 dB intensity and 1000 ms duration with 10 ms rise and fall times. The probability of the targets was 0.2. Inter-stimulus intervals (ISI) were changing randomly between 2500 and 3500 ms (mean 3000 ms). The subjects were instructed to count mentally the target stimuli. A total number of 150 trials with 120 standard and 30 target stimuli were recorded.

(3) Novelty paradigm: The same types of target and non-target stimuli as in paradigm 2 were applied with the addition of 30 different environmental sounds in a random order to create the novelty effect. The novel stimuli were digitized sounds obtained partly from the internet and partly digitized in our laboratory and presented using the sound card of a PC that also generated the standard and target tone bursts. The sounds were cut at 1000 ms to obtain a stimulus duration equal to the standard and target stimuli and mean intensities of the sounds were equalized to that of the standard and target stimuli (70 dB) using a normalization procedure, so that the root mean square (RMS) value of each sound waveform was set equal to the RMS amplitude of the tone burst used as target tone. The probabilities of the target and novel stimuli presented with ISIs randomly changing between 2500 and 3500 ms were 0.15 each. The subjects were instructed again to count mentally the target stimuli as in paradigm 2. A total number of 200 trials with 140 standard, 30 target and 30 novel stimuli were recorded.

(4) CNV paradigm: In each trial, two tone bursts of 50 ms duration and 10 ms rise and fall times were applied with an interval of 1250 ms. This pattern was repeated 35 times. The intertrial interval was 7000 ms. The first stimulus (warning stimulus) was a tone burst of 1000 Hz, whereas the second stimulus (imperative stimulus) requiring the subject to press a button as fast as possible, was a tone burst of 2000 Hz. A total number of 35 trials were recorded.

MMN was assessed by subtracting responses to standard stimuli of the passive oddball paradigm (paradigm 1) from the deviant responses. The mean amplitudes in the time window between 70 and 200 ms were measured. The P300 component was identified as the largest positive deflection between 250 and 500 ms in the target responses of the active oddball paradigm (paradigm 2), and the amplitude was measured relative to the pre-stimulus baseline. For the quantification of the P3a component, the amplitude of the largest positive peak between 240 ms and the individual P300 latency was measured relative to pre-stimulus baseline. CNV was quantified by computing the mean amplitude in the interval between 250 ms after the warning stimulus and the onset of the imperative stimulus.

For the first three paradigms (MMN, oddball and novelty paradigms) the ERPs were recorded from the F3, F4, Cz, P3, P4 sites of the international 10/20 system referenced to linked earlobes. Frontal and parietal areas, which are important locations for both P3b and P3a, were sampled at lateral locations (F3, F4, P3, P4) to be able to test a lateralization difference between both groups. For CNV signal, which is mainly localized in the fronto-central area, the lateral electrodes were placed in left and right frontal areas, and the other three channels were used to measure the signal in the midline locations, Fz, Cz and Pz. Electrooculogram (EOG) was recorded between the electrodes placed on the right outer epicanthus and upper medial rim. The data of passive, active oddball paradigms and novelty paradigm were amplified with a time constant of 1 s and CNV was measured with a time constant of 5 s. In all recordings, a low-pass filter set at 70 Hz was used. The data were digitized with an analog/digital (A/D) converter at a sampling rate of 256 Hz and 12 bit resolution, and stored on hard disk. All ERP sweeps exceeding ± 90 μV in amplitude were excluded automatically. ERPs were averaged off-line after an additional artifact-elimination was applied manually using EOG signal.

In a patient, the whole electrophysiological data set could not be evaluated due to the high artifact rate. After artifact elimination, the number of sweeps in the P3a recording of a patient was below 20. Similarly, the CNV recordings of three ALS patients and a control subject

were so artifactual that they could not be evaluated. Therefore, the total number of the valid experiments was 32 for N1, MMN and P3, 31 for P3a and 28 for CNV measurements.

2.3. Statistical methods

Mann–Whitney U, χ^2 and unpaired t-tests were used to evaluate the neuropsychological data.

All ERP measurements were evaluated using analyses of variance (ANOVA). First, the N1, MMN, P3b and P3a amplitude and latency differences between the patients and control group were tested using a one-way ANOVA on the data from the midline electrode, Cz. Then, the scalp distributions in antero-posterior (AP) and lateral (LAT) directions were tested using a repeated measures ANOVA design with two within-subject factors (AP: frontal vs. parietal; LAT: left vs. right) using the data from F3, F4, P3 and P4 electrodes, and the between-subject factor (group: patients vs. controls). Any significant interaction effects between the group factor and AP or LAT factors was further tested after normalizing the data according to the procedure described by McCarthy and Wood [44] and Naumann et al. [52]: each amplitude from each subject was divided by the mean amplitude obtained at Cz for each group. This procedure normalized the group effect and only the scalp distribution is compared across the groups.

For CNV recordings, first the midline amplitudes from Fz, Cz and Pz electrodes were statistically evaluated using a repeated measures ANOVA design for group and antero-posterior (AP) distribution factors (group: patients vs. controls; AP: Fz, Cz, Pz). Then in a second stage, lateralization factor is tested using a repeated measures ANOVA design with group and lateralization factors (group: patients vs. controls; LAT: F3 vs. F4).

Degrees of freedom (d.f.) were adjusted with the Greenhouse–Geisser epsilon coefficient for possible violations of the sphericity assumption and corrected P-values were reported. SPSS/PC program was used for all statistical analyses.

3. Results

No statistically significant differences were found between ALS patients and controls with respect to gender, age and education. MMSE scores were comparable and within the normal range in both groups (Table 3). Although the Hamilton depression rating scale (HDRS) scores were significantly higher in the patient group ($P<0.001$), the mean score (3.3 ± 2.3) was far below the cut-off value for depression and none of the patients were clinically depressed.

3.1. Neuropsychological test results

Test results are shown in Table 3. Almost all measures of the executive domain in the ALS group were significantly worse when compared with the control group. The majority of the attentional measures were also significantly worse in the patient group. Most of the registration and recall measures in CVLT were significantly impaired whereas recognition measures were comparable to controls. The patients named significantly fewer items in BNT. In the visuo-spatial domain, their performance was significantly worse in BLO and BD but not in BFR as compared with the control group.

3.2. ERP results

There were no significant differences in the task performance between the patients and control subjects in both the oddball (30.16 ± 1.95 vs. 30.31 ± 1.25; $F_{1,31}=0.06$, N.S.) and novelty (30.84 ± 2.57 vs. 31.92 ± 1.49; $F_{1,30}=2.23$, N.S.) paradigms. ERP results are summarized in Tables 4–6. Fig. 1 illustrates the grand averages of oddball target (P3b) responses of ALS patients (thick lines) and normal controls (thin lines). The P3b amplitude of the oddball target responses showed an overall typical parietal maximum (AP: $F_{1,30}=26.82$, $P<0.001$). Fig. 2 illustrates the grand averages of novelty P3a responses of ALS patients (thick line) and normal controls (thin line). The P3b latency was uniform across the leads, while P3a latencies were significantly shorter in frontal leads as expected (AP: $F_{1,29}=334.94$, $P<0.001$).

There were no differences in amplitudes and latencies of the N1 wave and amplitudes of the MMN between patient and control groups. However, the amplitudes of both P3b component (group: $F_{1,30}=4.78$; $P<0.05$) in the oddball target responses and the P3a component (group: $F_{1,29}=11.20$; $P<0.01$) of the responses to novel stimuli at vertex (Cz) were smaller in the patient group compared to the control group. In frontal and parietal channels, the significantly reduced P3b and P3a amplitudes ($F_{1,30}=7.6$, $P<0.01$ and $F_{1,29}=9.58$, $P<0.001$, respectively) in ALS patients supported further the view that both of these cognitive ERP components are overall attenuated in ALS. The group×antero-posterior scalp distribution interactions for both P3b and P3a amplitudes were non-significant after the vector length transformation procedure (Table 6b). However, there was a significant group×laterality interaction for P3a amplitude due to the stronger decrease of the P3a amplitudes on the right side ($F_{1,29}=10.69$, $P<0.01$). The P3a component had a significantly longer latency (group: $F_{1,29}=4.44$; $P<0.05$) in the patient group, whereas P3b did not differ in latency between patients and controls.

There was a significant increase in the mean CNV

Table 3
Neuropsychological test scores for patient and control groups

Test	Patients (n=20)	Controls (n=13)	$P<$
Screening tests			
MMSE	28±2	29±1	N.S.
HDRS	3.3±2.3	1±1	0.001
Attention			
WAIS-R DS—fwd	4.8±2	5.8±1.6	N.S.
WAIS-R DS—bwd	3.8±1.9	5.1±1.8	0.03
CPT—total correct	96±11	102±9	0.03
CPT—commissions	16±17	4±4	0.01
CPT—response latency	39±4.6	36±5.8	N.S.
Executive functions			
DRT	70±20.1	83±3.4	0.04
SDLT	6±6.7	11±7.2	0.03
Stroop 1	17±7	11±1.8	0.003
Stroop 5	42±22	29±7	0.02
Go–no-go commission (right hand)	5±3	1±1	0.0001
Go–no-go response latency (right hand)	46±8	44±6	N.S.
Go–no-go commissions (left hand)	3±5	1±1	N.S.
TMT A	99±62	55±27	0.01
TMT B	198±41	121±63	0.02
TMT B–A	126±37	66±44	0.01
FAS	18±12	26±8	0.02
Category naming (animals)	15±5.7	19±4	0.02
Language			
BNT (30 items)	18±4	24±4.2	0.001
Memory (CVLT)			
Registration measures			
Total of 5 trials	37±11	48±7	0.004
1st trial	4.4±1.4	6.2±2	0.01
5th trial	9±3	10±3	N.S.
Recall measures			
Short-delay free recall	8.5±3	9.7±2	N.S.
Short-delay cued recall	9±3	11.5±1.6	0.03
Long-delay free recall	8.3±3	11±2.5	0.02
Long-delay cued recall	9±3	12±2	0.01
Perseverations	7±4	3±3	0.01
Free recall intrusions	3.6±3	3.4±2.7	N.S.
Cued recall intrusions	2.6±1.9	2.1±1.6	N.S.
Recognition measures			
Recognition	14.5±1.6	13.9±1.7	N.S.
Discriminability (%)	87.5±12	92±6	N.S.
False positives	4±6	1.5±1.5	N.S.
Visuo-spatial processing			
BLO	18±7.1	23±4.2	0.01
BFR	40±4.8	43±6.3	N.S.
WAIS-R BD	14±7	24.5±8.8	0.002

N.S., non-significant

amplitudes in patients (group: $F_{1,26}=4.58$; $P<0.05$) in contrast to the decreased amplitudes of P3a and P3b waves. Fig. 3 illustrates the grand averages of CNVs of ALS patients (thick lines) and normal controls (thin lines). The CNV showed a typical fronto-central topography (AP: $F_{2,52}=7.80$, $P<0.001$). The increase of the CNV amplitude in the patient group was most prominent in F3 and F4 ($F_{1,26}=10.27$, $P<0.001$), whereas almost no difference was found between the patients and controls in the parietal location.

Table 4
(a) Mean values and standard deviations of amplitudes and latencies of P300 and P3a event-related potentials. (b) Mean CNV amplitudes

Leads	P3a amplitude (μV)		P3a latency (ms)		P300 amplitude (μV)		P300 latency (ms)	
	Patient	Control	Patient	Control	Patient	Control	Patient	Control
(a)								
F3	6.6±3.4	11.8±6.0	291±35	268±17	5.5±3.5	8.1±5.1	352±42	338±27
F4	6.9±3.2	10.8±6.2	292±34	267±17	5.1±3.6	7.5±4.9	352±41	337±27
Cz	7.1±4.4	14.5±7.8	292±34	271±18	6.8±3.1	9.6±4.2	352±40	334±25
P3	6.9±4.5	14.3±7.3	304±34	286±17	6.8±3.1	11.7±4.3	353±40	335±23
P4	7.8±4.7	14.0±7.1	304±33	286±16	6.7±2.3	11.2±4.9	353±38	334±22

(b)

Leads	Mean CNV amplitude (μV)	
	Patient	Control
F3	−9.8±5.8	−4.3±3.1
F4	−9.4±6.1	−4.0±4.9
Fz	−8.8±4.1	−5.8±3.8
Cz	−9.6±5.2	−5.4±3.7
Pz	−5.1±4.1	−4.1±3.0

4. Discussion

4.1. Downstream attentional processes are intact but upstream processes are impaired in early ALS

The results of the study revealed a robust and consistent impairment in executive and some attentional functions both of which are under the control of frontal networks. Findings not readily explicable with a frontal network involvement were either not consistent or presumably secondary to the primary impairment in attention. In consistence with our findings, previous reports on cognitive dysfunction in ALS focus mainly on attention and impairment in other cognitive domains secondary to attentional impairment [4,43]. In the present study, the absence of any significant differences between the patients and control subjects in N100 and MMN measurements suggests that impairment in attention is not due to a primary vigilance or arousal problem and downstream attentional processing is intact. Gil et al. observed normal N100 amplitude in an oddball paradigm when ALS patients were not depressed [28]. Similarly, Vierrege et al. attributed their findings of attenuated N100 in an auditory ERP recording to the depressive mood of their ALS patients [72]. In contrast, Münte et al. could not record a demonstrable P1 component in visual evoked potential

Table 5
(a) Summary of one-way ANOVA results for the N1, MMN, P3A and P300 amplitude and latencies at midline location, Cz, between patient and control groups. (b) Summary of repeated measures ANOVA (two control vs. patient groups×two antero-posterior distribution×two lateral distribution) for the P3A and P300 amplitudes, vector transformed amplitudes and latencies

(a)	N1		MMN	P3a		P300	
	Ampl.	Latency	Ampl.	Ampl.	Latency	Ampl.	Latency
d.f.	(1/31)	(1/31)	(1/31)	(1/30)	(1/30)	(1/31)	(1/31)
F	0.01	3.14	0.88	11.20**	4.38*	4.78*	1.90

(b) Factor	P3a			P300		
	Ampl.	Vector	Latency	Ampl.	Vector	Latency
d.f.	(1/29)	(1/29)	(1/29)	(1/30)	(1/30)	(1/30)
Group	9.58***		4.44*	7.60**		1.71
AP	10.86**	6.60*	334.90***	26.82***	21.37***	0.33
LAT	0.03	0.94	0.086	3.04	2.17	0.08
G×AP	4.56*	1.02	14.83**	5.16*	1.79	1.98
G×LAT	11.47**	10.69**	1.04	0.52	0.15	0.75
AP×LAT	3.71	3.54	0.07	0.28	0.31	0.01
G×AP×LAT	0.05	0.21	0.83	0.07	0.12	0.01

*$P<0.05$; **$P<0.01$; ***$P<0.001$.

Table 6
(Top panel) Summary of ANOVA (two control vs. patient groups×three midline electrodes [Fz,Cz,Pz]) for the CNV amplitudes. (Bottom panel) Summary of ANOVA (two control vs. patient groups×two lateral electrodes [F3,F4]) for the CNV amplitudes

CNV	
Factor (d.f.)	*F*
Group (1/26)	4.58*
AP (2/52)	7.80***
G×AP (2/52)	1.78
Group (1/26)	10.27***
LAT (1/26)	0.12
G×LAT (1/26)	0.00

*$P<0.05$; **$P<0.01$; ***$P<0.001$.

experiments in their patient groups, suggesting an early sensory involvement in ALS [47–49]. Yet, their patient group had a relatively long disease duration with a mean of 4.1 years [47]. Normal N100 latencies and amplitudes observed in the present study provide evidence for intact primary sensory processing. Accordingly, the decrease in P3a and P3b amplitudes in patients might be interpreted as a result of a dysfunction of the more upstream attentional network, which is thought to be largely under prefrontal control [40]. Nasman and Dorio suggested that decreased P300 amplitude in patients with prefrontal pathology might be due to ineffective prefrontal support to shifting attention to task-relevant stimuli [51]. This dissociation in attentional processing, i.e. intact downstream, but impaired upstream processing, has its parallels in comparable forward

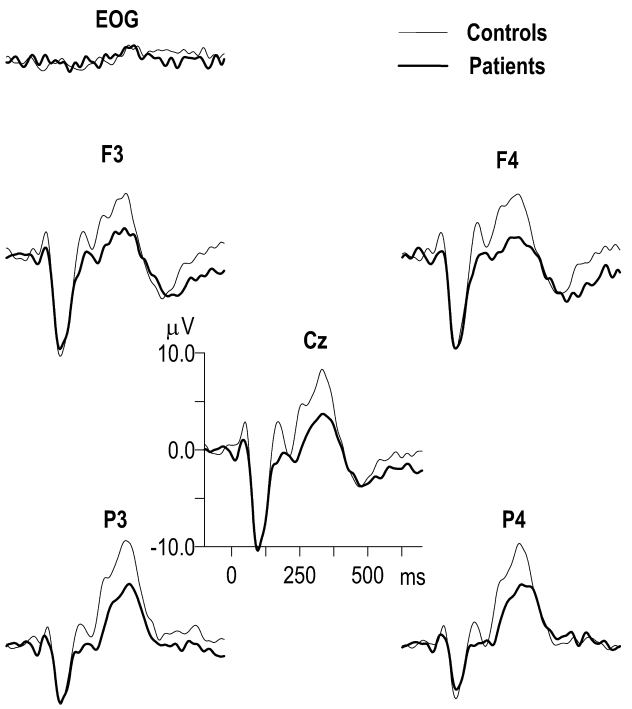

Fig. 1. The grand averages of oddball target (P3b) potentials of ALS patients (thick lines) and normal controls (thin lines).

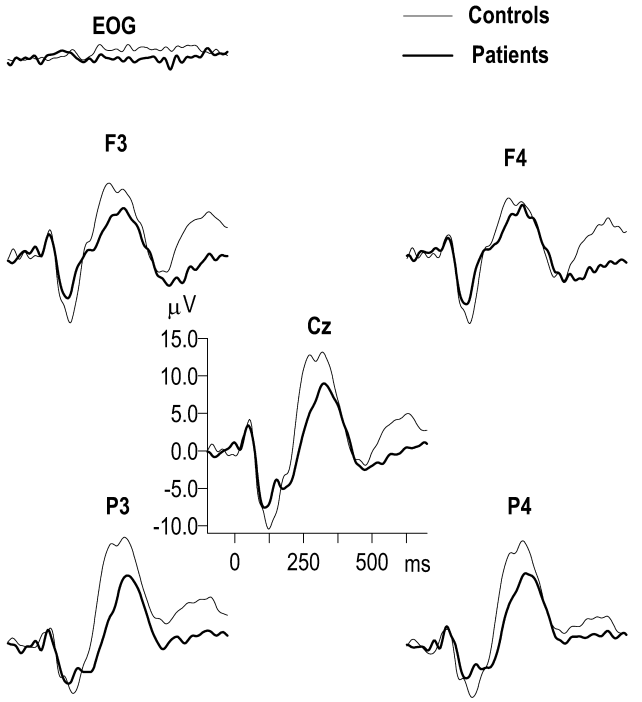

Fig. 2. The grand averages of novelty P3 (P3a) potentials of ALS patients (thick lines) and normal controls (thin lines).

but significantly shorter backward digit span of the patient group. Forward span is an index of global attention, whereas the performance of backward span necessitates the on-line holding of the original series, in order for it to be

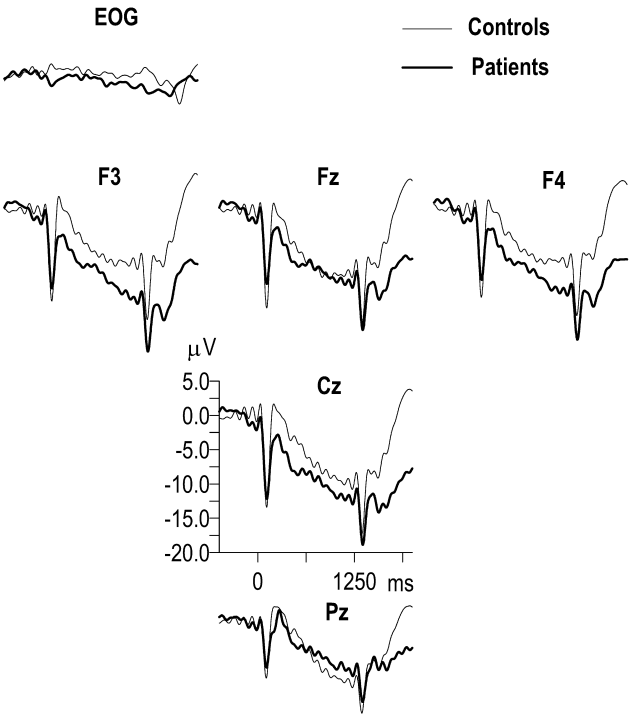

Fig. 3. The grand averages of CNVs of ALS patients (thick lines) and normal controls (thin lines).

recited in the reverse order, hence an intact working memory.

4.2. Linguistic processes

Decreased performance in BNT was suggestive of a subtle problem in linguistic processing, since none of the patients had other language problems. Left extra-perisylvian dorsolateral prefrontal dysfunction, the major neural substrate of the so-called 'transcortical motor aphasia' can give rise to deficits in both word-list generation and confrontation naming [8] and may explain the naming deficit observed in this study. Demented or non-demented ALS patients may occasionally present with aphasia [10,17]. Naming deficits in non-demented ALS patients were also reported previously [43].

4.3. Visuo-spatial processes

Significant impairment in visuo-spatial processing in ALS patients was reported previously [31]. In the present study, performance in BLO (Benton's line orientation) and BD (Weschler block design) were impaired whereas BFR (Benton's facial recognition) seemed to be intact. This could be attributed to the relative difficulty of the former group of tests. Alternatively, this dissociation could be due to different strategies and distinct neural pathways underlying the performances of these tests. BD is a visuo-constructive test, which necessitates visuo-motor integration, as well as planning, strategy testing and behavioral persistence, which are all under executive control. BFR and BLO are conventional 'pure' visuo-perceptual tests thought to be mediated through right parietal cortex, but BFR through ventral and BLO through dorsal visual processing pathways. The final target of the former (object recognition) pathway is the hippocampus and of the latter (spatial analysis) is the frontal eye field. Thus the dissociation could be due to the influence of a dysfunctioning prefrontal system on particular visuospatial processing networks (i.e. dorsal).

4.4. Episodic memory

In the episodic memory domain, CVLT findings revealed a clear-cut registration and recall deficit, whereas recognition was intact. This profile is similar to those seen in the so-called 'subcortical dementias' such as progressive supranuclear palsy [69] and Huntington's disease [21]. This type of memory impairment is thought to be due to insufficient contribution of prefrontal cortex to mnestic processes, since long-term storage is mediated through limbic, whereas retrieval is mediated through prefrontal structures. Retrieval, rather than storage deficit is inferred from the relative sparing of recognition in the context of a defective recall. Massman et al. reported similar results in CVLT [43], whereas others suggest that memory impairment in ALS is due to limbic involvement [34,55]. Our findings are, however, more in favor of a secondary memory problem rather than limbic involvement.

4.5. Executive functions

Tests assessing executive functions revealed consistent and significant impairment in the patient group. As an electrophysiological correlate of this impairment, latency of P3a was prolonged and amplitude was reduced. The findings of decreased P3a amplitude and increased P3a latency suggest impairment of novelty detection mechanisms [24,64], which are associated with the dorsofrontal, orbitofrontal and anterior cingulate (AC) cortices [11,64]. This may explain the changes of P3a in ALS since AC is presumed to be one of the main generators of P3a [11].

4.6. CNV changes support the hyperexcitability hypothesis of the pathophysiology of ALS

Of particular interest is the increase of the CNV amplitude in patients compared to controls. At first glance, the increased activity in CNV generators in the prefrontal cortex seems to contradict with the decreased performance in tests related to frontal functions, which is supported electrophysiologically by decreased amplitudes of P3a and P3b along with increased P3a latency. However, a more in-depth analysis of the pathophysiology of ALS indicates that these seemingly contradictory results might be meaningful and important in understanding the neurophysiological basis of the disease. One of the hypotheses about the pathogenesis of ALS is excessive glutamatergic excitotoxicity [61]. Several neurochemical and neurophysiological studies revealed hyperexcitability of the corticomotor system in ALS [23,56,65]. Increased extracellular glutamate could result in hyperexcitability in cortical or spinal motorneurons [62]. Surface-negative slow (DC) potential shifts such as CNV have been shown to reflect the increased excitability of the cortical neurons [15,59]. Hence, the increased CNV amplitudes might be due to the hyperexcitability of the corticomotor system. Additionally, a number of studies have shown that P300 potentials indicate widespread inhibition (disfacilitation) of cortical neural excitability [22,60]. This was supported in a study with depth electrodes in patients with temporal lobe epilepsy, which showed reduced limbic P300 amplitudes on the side of the epileptogenic focus [29]. Considering the neuronal generation mechanisms of 'negative' CNV shifts and 'positive' P300 waves, we suggest that the increased CNV amplitudes and reduced P3b and P3a amplitudes on frontal regions of ALS patients are in accordance with the corticomotor hyperexcitability hypothesis. These results in early and less handicapped ALS patients might change towards a reduction in CNV in later stages of the disease due to extensive neuronal loss.

Another possible explanation for this finding could be

the need for higher excitability or facilitation in premotor/motor areas in ALS, to generate the level of neural signals in the corticomotor system that is necessary to produce the motor tasks in response to the imperative stimulus.

5. Conclusion

In conclusion, the results of the neuropsychological and ERP measurements indicate a predominantly frontal dysfunction in non-demented patients with sporadic ALS. The infrequent report of clinically overt cognitive deficits may be due to the fact that cognitive problems might be masked in the face of severe motor impairment in ALS and detailed neuropsychological assessment may be necessary to uncover mild cognitive problems. ERPs can be used as an adjunct to neuropsychological testing in the assessment of cognitive deficits in ALS. The early stage of disease in our patients enabled us to investigate the earliest profile of cognitive dysfunction. It is possible that in later stages ALS patients may have further cognitive involvement and 'frontal lobe dementia' may represent the extreme end of the spectrum. It is important for the health care professionals and family members to be aware of potential frontal dysfunction and their implications in ALS patients.

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