Selective attention is impaired in amyotrophic lateral sclerosis—a study of event-related EEG potentials

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Abstract

In humans, selective attention is assumed to be under control of the frontal lobe. A significant proportion of patients with amyotrophic lateral sclerosis (ALS) shows impairments in various tasks touching frontal lobe function. We, therefore, undertook a study of event-related EEG potentials (ERPs) in eight non-demented ALS patients in order to investigate a possible deficit of auditory selective attention: tones were presented in random sequence to the left or right ear, one of which was to be attended. The negative shift of the ERPs evoked by attended tones in relation to unattended tones (‘processing negativity’: PN) was smaller in ALS patients than in age-matched healthy control persons. This was true for Fz and Cz and for both a slow and a fast presentation rate of the tones. In the patients, reduced PN amplitude correlated with functional motor impairment. The utility of ERP testing to assess impaired frontal lobe function is shown for the first time in ALS patients. The results of our study fit to recent positron emission tomography (PET) and fMRI data.

Keywords: Amyotrophic lateral sclerosis; Event-related potential; Neuropsychology; Frontal lobe function; Selective attention

1. Introduction

Evidence is increasing that patients with sporadic amyotrophic lateral sclerosis (ALS) have non-motor abnormalities from cortical dysfunction outside the primary motor areas [1,26,27,59]. Cross-sectionally, a cognitive disturbance in ALS is found in about 35% of cases [35]. The most frequent impairments have been observed in neuropsychological tests of verbal reasoning, visual attention, picture sequencing and category formation [2,11,16,17,59]. There are also memory and learning deficits in tasks on prose and picture recall, word list and verbal paired associate learning [1,11,16,17,26,35]. Corresponding to these findings the regional cerebral blood flow (rCBF) at rest is focally reduced in frontal [30,64], hippocampal [64], and anterior temporal [59] areas of non-demented ALS patients, as is glucose utilization over frontal and fronto-basal regions when assessed by positron emission tomography (PET) [34].

In PET investigations of healthy subjects, verbal fluency tasks both in the oral [26,27,34] and written form [1] activate the rCBF in the dorsolateral prefrontal, the bilateral prefrontal, and the anterior cingulate cortex [15,47]. The rCBF in the latter area is increased in healthy probands also during the selective attention task of the Stroop colour/word interference paradigm [9,46]. Lesions of the dorsolateral prefrontal cortex have been linked to impaired response inhibition during attention demanding neuropsychological tasks [12,50]. Thus, both the dorsolateral prefrontal and the anterior cingulate cortex have a role in response selection and direction of attention. Importantly, in PET studies of ALS patients, both regions show reduced rCBF either at rest [26] or during activation [1]. We, therefore, hypothesized that selective attention would be impaired in cross-sectionally investigated non-demented ALS patients.

The use of event-related EEG potentials (ERPs) allows the measurement of selective attention without interference from speech or other motor impairment of ALS. The method provides the opportunity to assess selective attention in a domain different from the visual. The ‘processing negativity’ (PN) [40] is supposed to reflect auditory selective attention: two series of tones are presented in random sequence, one of which is to be attended to. The ERPs evoked by the attended tones are negatively shifted in
relation to those of unattended tones [40]. The shift may already well be visible at the peak of the N1 wave (at about 100 ms) [21] and may last for several 100 ms. It is called PN [39,40] and attributed to the subjects’ maintenance of a vivid internal template of the attended stimulus (the ‘attentional trace’) [39,40]. Two components have been distinguished: the first with a topographic focus at Cz may reflect the matching of the present tone with the internal template and may be generated within the auditory cortex [18,40]. A second subcomponent at 300 to 500 ms (focused at Fz) is thought to represent the updating of the internal template, possibly generated by a transient cerebral arousal in response to a relevant stimulus [40]. The source of this component is assumed to be situated deep-frontally [18]. According to the above considerations, a decrease of the PN, particular of its late component, was expected for the present experiment in non-demented sporadic ALS patients.

2. Materials and methods

2.1. Subjects

Eight right-handed in-patients with clinical and electrophysiologic signs of combined upper and lower motor neuron involvement pointing to a diagnosis of definite or probable ALS [69] were studied. Their demographic data are presented in Table 2. Median disease duration of the patients was 26 months (range: 11 to 132). Their mean score on the Norris scale items 1 to 22 [43] was 49 ± 16 (range: 16 to 64). Their mean score on the ALS Functional Rating Scale [60] was 29 ± 12 (range: 8 to 40). No patient had dementia according to history, clinical and mini-mental state examination [14] or abnormalities on routine EEG recording and magnetic resonance tomography exceeding those of age-related changes. No patient was on medication relevant to CNS function except for five patients who took riluzole at a daily dose of 100 mg for periods between 11 and 40 weeks prior to this study. Details of clinical features of the patients are given in Table 1.

Eight age-matched right-handed control subjects were gathered from a panel of healthy volunteers. Their demographic data are presented in Table 2. These subjects had neither history nor signs of brain damage, neurologic or psychiatric disease, drug or alcohol abuse, of severe hypertonia. None of the controls took drugs likely to affect vigilance or mental capacities. Handedness was tested formally, hypacusis was excluded clinically in all participants. The number of education years was 9.6 ± 1.7 years (range: 8 to 13) in the patients and 11.5 ± 1.9 years (range: 8 to 13) in the controls (ANOVA: F(1,14) = 4.29; p = 0.06). After full explanation of the procedure all subjects gave their informed oral consent to participation.

2.2. Stimuli and procedure

A total of 300 tones/block were generated by a PC and were presented via earphones (Sony CD 250) in random sequence either to the left or to the right ear. To enhance between-channel discriminability, left ear tones were always low (500 Hz), whereas right ear tones were high (1000 Hz). A total of 90% of all tones had a duration of 50 ms (‘standards’), 10% were markedly longer (200 ms; ‘deviants’). In the first and fourth block, tones were presented ‘slowly’, i.e., separated by a mean onset-to-onset interval of 1 s randomly varying between 800 and 1200 ms; in the second and third block, presentation was ‘fast’, i.e., with 0.5-s interval (varying between 400 and 600 ms). The subjects’ task was to attend to tones in one ear (left ear in blocks 1 and 2, right ear in blocks 3 and 4) and to press a button in response to ‘targets’, defined as the infrequent deviants presented in that ear.

2.3. Recording and data processing

Sintered Ag/AgCl electrodes (Picker-Schwarzer) were affixed at Fz, Cz, and Pz, at both mastoids, above and

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Table 1

Clinical characteristics of eight ALS patients

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (years)/sex</th>
<th>Disease duration (months)</th>
<th>Pseudobulbar involvement (UMN)</th>
<th>Bulbar involvement (LMN)</th>
<th>Wasting</th>
<th>Fasciculations</th>
<th>Spasticity</th>
<th>Hyperreflexia</th>
<th>Babinski sign</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69/m</td>
<td>45</td>
<td>-</td>
<td>+</td>
<td>UL/LL</td>
<td>UL/LL</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>57/m</td>
<td>29</td>
<td>+</td>
<td>-</td>
<td>UL</td>
<td>UL</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>45/f</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>UL</td>
<td>UL/LL</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>65/m</td>
<td>132</td>
<td>+</td>
<td>+</td>
<td>UL</td>
<td>UL/LL</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>68/m</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td>LL</td>
<td>LL</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>46/f</td>
<td>11</td>
<td>-</td>
<td>+</td>
<td>UL/LL</td>
<td>LL</td>
<td>+</td>
<td>+</td>
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<td>8</td>
<td>51/f</td>
<td>54</td>
<td>+</td>
<td>+</td>
<td>UL/LL</td>
<td>UL/LL</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

UL = upper limb.
LL = lower limb.

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below the right eye and 1 cm laterally of the right and left eye each. The mastoid electrodes were shunted via a 5-kΩ resistor and served as references for Fz, Cz, and Pz, while the vertical and horizontal electrooculogram (EOG) were recorded bipolarly. EEG and EOG were amplified by a Nihon Kohden 4421 within the frequency limits of 0.032 Hz (= 5 s time constant) and 70 Hz. The data were continuously digitized at 200 Hz, using a Pentium microcomputer. Out of this recording, 800 ms epochs were selected off-line from 100 ms before each tone to 700 ms after each tone. This off-line procedure was necessary due to overlap between epochs. The electrophysiologic data were screened for artifacts with own software that looked in the EOG for blink potentials and other eye-movements, and in all recordings for zero lines, out-of-scale values and amplitudes larger than 100 μV peak-to-peak within 500 ms. Since the instruction to refrain from blinking constitutes a second task that may affect ERP amplitudes to the primary task [52], no such instruction was given. Nevertheless, trials contaminated with blinks were not corrected for this artifact as in previous studies of this laboratory but were rejected from analysis, on request of one referee of this paper, as were trials contaminated with other artifacts and with incorrect responses.

EEG and EOG potentials of each subject were pooled over side of the ear to be attended, i.e., over blocks 1 and 4 for slow presentation and blocks 2 and 3 for fast presentation. They were digitally filtered with a 30-Hz low pass and were averaged separately for eight categories, which were two channels (attended, ignored), two stimuli (standards, deviants) and two presentations (slow, fast). The number of trials included in the averages of the standard stimuli ranged between 37 and 259 (mean 82) trials in the patients, and between 43 and 256 (mean 67) trials in the control group. The few number of trials included in the averages of the deviant stimuli precluded systematic analysis of those averages. For measurement of the PN, differences were formed by subtracting the average of the ignored standard tones from the average of the attended standard tones, separately for the two presentation rates. After inspection of the grand means of these difference waves, PN was quantified by computing the mean amplitude of a window spanning from 175 to 300 ms after tone onset at Fz and Cz. The N1 was measured in the Fz and Cz standard averages as largest negative peak 70 to 140 ms, P2 as the largest positive peak 150 to 250 ms after tone onset.

To assess differences between patients and controls, data were submitted to analyses of variance with ‘group’ as between-subjects factor and with the two repeated-measurement factors of ‘presentation rate’ (slow/fast) and ‘recording site’ (Fz/Cz). Omitting the factor ‘recording site,’ similar analyses of variance were computed on response times.

2.4. Neuropsychological testing

In a separate session several days before or after the electrophysiologic recording a neuropsychological test battery was applied to each participant. This comprised the German versions of the following.

(1) Short form of the revised Wechsler Adult Intelligence Scale (WAIS-R) [66] using the subtests ‘information’, ‘similarities’, ‘picture completion’, and ‘block design’ to assess general intelligence.

<table>
<thead>
<tr>
<th>Patients (N = 8; 4 f, 4 m)</th>
<th>Controls (N = 8; 7 f, 1 m)</th>
<th>F-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.4 ± 10.6 (43–68)</td>
<td>59.3 ± 11.4 (36–73)</td>
<td>(1,14) = 0.03</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>105.6 ± 14.6 (88–132)</td>
<td>116.0 ± 19.5 (86–136)</td>
<td>(1,13) = 0.51</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>113.0 ± 15.4 (92–136)</td>
<td>105.9 ± 14.5 (79–127)</td>
<td>(1,13) = 0.85</td>
</tr>
<tr>
<td>Total IQ</td>
<td>109.3 ± 14.3 (92–134)</td>
<td>110.3 ± 18.2 (82–134)</td>
<td>(1,13) = 0.01</td>
</tr>
<tr>
<td>Auditory verbal learning test (AVLT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total learning score</td>
<td>45.9 ± 9.0 (33–62)</td>
<td>49.8 ± 8.3 (34–60)</td>
<td>(1,13) = 0.76</td>
</tr>
<tr>
<td>Discrepancy score</td>
<td>3.0 ± 2.2 (1–6)</td>
<td>2.6 ± 1.5 (1–4)</td>
<td>(1,13) = 0.16</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>9.3 ± 3.3 (5–13)</td>
<td>10.6 ± 1.5 (8–13)</td>
<td>(1,13) = 1.10</td>
</tr>
<tr>
<td>Recognition score</td>
<td>13.6 ± 1.5 (11–15)</td>
<td>13.1 ± 1.6 (11–15)</td>
<td>(1,13) = 0.32</td>
</tr>
<tr>
<td>Number of recognition errors</td>
<td>2.6 ± 4.3 (0–12)</td>
<td>0.4 ± 0.7 (0–2)</td>
<td>(1,13) = 2.03</td>
</tr>
<tr>
<td>FAS test</td>
<td>32.0 ± 4.5 (26–38)</td>
<td>37.3 ± 9.7 (18–47)</td>
<td>(1,11) = 1.26</td>
</tr>
<tr>
<td>Number of errors</td>
<td>5.4 ± 5.1 (0–12)</td>
<td>2.3 ± 1.8 (0–6)</td>
<td>(1,11) = 2.61</td>
</tr>
<tr>
<td>Total fluency score</td>
<td>63.0 ± 6.8 (53–68)</td>
<td>70.6 ± 21.2 (41–101)</td>
<td>(1,10) = 0.55</td>
</tr>
<tr>
<td>Number of errors</td>
<td>4.8 ± 5.3 (0–12)</td>
<td>3.0 ± 3.1 (0–10)</td>
<td>(1,10) = 0.47</td>
</tr>
<tr>
<td>Trail making test</td>
<td>44.8 ± 12.7 (24–60)</td>
<td>43.1 ± 6.5 (34–52)</td>
<td>(1,12) = 0.11</td>
</tr>
<tr>
<td>Stroop test</td>
<td>10.2 ± 10.4 (–6–22)</td>
<td>11.3 ± 3.6 (5–17)</td>
<td>(1,12) = 0.08</td>
</tr>
<tr>
<td>Trail C–B</td>
<td>52.0 ± 51.8 (21–155)</td>
<td>28.6 ± 11.3 (19–52)</td>
<td>(1,12) = 1.57</td>
</tr>
<tr>
<td>Depression scale</td>
<td>60.4 ± 5.3 (53–70)</td>
<td>50.3 ± 3.3 (46–55)</td>
<td>(1,13) = 20.67</td>
</tr>
</tbody>
</table>
(2) AVLT [33] to assess immediate memory span, verbal learning, recall memory following an interference task, and recognition.

(3) Controlled Oral Word Association Test (FAS test) [33,56]. A FAS score was formed from the sum of correct words with the letters F, A, and S; an error score was calculated from the sum of errors (repeats, variations, intrusions). Semantic fluency was assessed using the category ‘foods’ [32]. Alternating fluency was tested with a semantic/letter initial task (‘animals/L’) [13]. For each category, scores were formed from the sum of correct words; an error score was calculated from the sum of errors. From the sum scores (FAS + foods + animals/L) a total fluency score and a total error score were determined.

(4) Trail Making Test [45] to measure perceptual speed. The raw value of the time required to complete the task was transformed into T-scores.

(5) Stroop Colour Word Test [3] to measure executive function. Test scores were the time required to complete each task (A: speed of colour reading; B: speed of naming coloured bars; C: speed of colour naming in coloured words). The naming score was the difference between trial B and trial A; the interference score was the difference between trial C and trial B [55]. Low values on ‘interference’ indicate low ‘selectivity of attention’, i.e., marked interference.

(6) Depressive mood was assessed with the ‘Depression Scale’ [70].

To assess verbal IQ the WAIS was always presented at the start of the session. All other tests were administered in a counterbalanced order to control for fatigue effects. Due to severe bulbar and extremity involvement patient number 8 did not participate in neuropsychological testing at all. Bulbar involvement hindered FAS performance in patients number 2 and 4. Patient number 1 was not able to complete the Trail Making Test, and patient number 4 could not perform the Stroop. Clinical (P.V.), neurophysiologic (B.W.) and neuropsychological assessments (I.H.) were done by different observers each of whom was blind for the results of the other assessments (except for group status). Mean values of demographic data and of neuropsychological test variables were compared using ANOVA.

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**Fig. 1.** Difference potentials of attended-minus-unattended standard stimuli. These potentials were obtained by subtracting the potentials evoked by standard tones in the unattended ear (Figs. 2 and 3, right-hand side) from the standard tones in the attended ear (Figs. 2 and 3, left-hand side). Grand means over eight patients (bold) and eight control subjects (thin). Left: Blocks with slow stimulus rate (1/s). Right: Blocks with fast stimulus rate (2/s). EOG is the electrooculogram (for control of transmission of ocular potentials to the EEG). Fz, Cz, Pz are frontal, central, parietal midline sites on the scalp. x-axis zero is tone onset. PN was measured as the mean amplitude 175 to 300 ms after tone onset in each subject’s average potential.
Correlations between demographic data, electrophysiologic and neuropsychological test variables were computed using Pearson’s correlation coefficient. For all statistical comparisons a \( p \)-value of \( \leq 0.05 \) was considered significant.

3. Results

Clinical and neuropsychological data for patients and controls are given in Table 2. Both groups did not differ in age, IQ, verbal memory, verbal fluency, the Trail Making, and the Stroop test. The patients had significantly higher scores on the ‘Depression Scale’ than controls.

3.1. Response times and errors

Patients responded more slowly than controls (534 ± 189 ms vs. 436 ± 49 ms with slow presentation; 560 ± 187 ms vs. 433 ± 53 ms with fast presentation). These differences were not statistically significant due to large variations between patients. Within both groups reaction times were not different when values for slow presentation were compared to those for fast presentation. Reaction times for both presentation rates correlated with each other in both patients (\( r = 0.98, \ p < 0.001 \)) and controls (\( r = 0.77, \ p = 0.026 \)). In patients, reaction times for both presentation rates were higher with more disease impairment when rated by either the Norris score (slow: \( r = -0.85, \ p = 0.008 \); fast: \( r = -0.78, \ p = 0.023 \)) or the ALS Functional Rating Score (slow \( r = -0.84, \ p = 0.009 \); fast: \( r = -0.78, \ p = 0.024 \)). Mean error rate (‘false alarms’, i.e., keypresses when there was no deviant tone to be attended 150 to 1500 ms prior to keypress) between groups was neither different for slow (patients 2.1 ± 3.3 vs. controls 0.1 ± 0.4; \( F_{1,14} = 2.96, \ p = 0.11 \)) nor for fast presentation (patients 2.3 ± 3.4 vs. controls 0.0 ± 0.0; \( F_{1,14} = 3.48, \ p = 0.08 \)). For fast presentation, the error rate of the patients correlated with the Norris score (\( r = 0.78, \ p = 0.022 \)).

3.2. Processing negativity

Difference waveforms (attended standards minus unattended standards) for patients and controls for both pre-
sentation rates are displayed in Fig. 1. PN amplitudes were smaller in patients than in controls ($F_{1,14} = 7.4, p = 0.02$). This was true both for Fz and for Cz amplitudes and both for slow and fast presentation (all interactions of these variables with group factor were insignificant; $F_{1,14} \leq 2.02, p > 0.17$). No group differences emerged for the epochs after 300 ms. Since PN is computed as the difference ‘attended minus unattended’, it was of interest whether the group effect was due to the attended potentials being more negative or the unattended potentials being more positive in the control group than in the patients. However, neither of these alternatives approached significance, obviously due to the overlapping P2 component (Figs. 2 and 3). In both groups, correlations between PN and clinical and neuropsychological variables were observed only for slow presentation rate: the PN at Fz was lower with a higher score on the Norris ($r = -0.78, p = 0.02$) and the ALS Functional Rating Scale ($r = -0.85, p = 0.061$), i.e., the PN was lower in the more impaired ALS patients. In the control group, PN amplitudes at Cz were higher with a lower error rate in the FAS score ($r = 0.85, p = 0.007$) and with a lower error rate in total fluency ($r = 0.89, p = 0.003$).

The five ALS patients under riluzole medication had a higher PN amplitude than the three patients without riluzole ($F_{1,6} = 6.11, p = 0.048$). Compared to controls the five patients tended to have a smaller PN ($F_{1,11} = 3.05, p = 0.11$), while the three drug-free patients had a significantly smaller PN ($F_{1,9} = 6.79, p = 0.029$). For slow presentation rate (at Cz) there was a tendency for a correlation between PN and cumulative riluzole dosage for the five treated patients ($r = -0.750, p = 0.144$). There were no differences between patients with and without riluzole treatment with regard to the Norris and ALS Functional Rating Scale, to Stroop performance and depression.

### 3.3. Additional analyses

Quantitative analysis confirmed the impression from Fig. 2 about group differences for the N1 component. The N1 amplitude was lower in the patients than in the controls ($-6.1 \mu V$ vs. $-9.8 \mu V$: $F_{1,14} = 11.5, p = 0.004$) without differences between recording sites and presentation rates. Overall and irrespective of group status, the N1 amplitude was larger with slow than with fast presentation rate, presumably due to refractoriness [41]. It tended to be larger with attended than with unattended stimuli probably to the overlapping PN. No effect was significant for N1 latency and P2 latency. The only effect of group on P2 amplitude

![Fig. 3. Potentials evoked by standard stimuli in the blocks with fast stimulus rate (2/s). See legend of Fig. 2 for further details.](image-url)
was the interaction of presentation rate × recording site × attended/unattended × group \((F_{1,4} = 4.9, \ p = 0.04)\), because amplitudes were of equal size at Fz and Cz except for attended stimuli at slow presentation rate in the control group. Here, Cz amplitudes were larger than Fz amplitudes. There were no correlations between either the N1 and P2 component measures and any clinical or neuropsychological variable.

4. Discussion

As a measure of auditory selective attention the PN is reduced in our sample of sporadic non-demented ALS patients. The result is remarkably robust, since it is already observed in a group of eight patients. The finding holds true for both recording sites and for both modes of stimulus presentation. Though there were more women in the control than in the patient group, present knowledge does not support sex influences on selective attention findings. There is also no evidence that the differential intake of the CNS-acting drug riluzole might explain the PN reduction [52]. Rather, riluzole appeared to have a somewhat ‘ameliorating’ effect on the PN in those patients who took the drug for different periods of time prior to this study. Nor is the PN result explained by abnormalities of the peripheral auditory pathway [36,51], the auditory cortex, and, specifically, the superior temporal gyrus in ALS. The latter region is considered to be the generation area for the early component of the PN [18,40] and also for the N1 [41,53,54].

One should note that our PN result is not due to differences in the N1 amplitude [37]: the latter arises at already 100 ms, whereas the PN difference is in the range of 175–300 ms. Nevertheless, both the amplitude of the N1 wave and the PN were attenuated among our patients. A relevant factor in this context could be depressiv mood, since our ALS patients scored higher on depression than the controls. Relevant factors for the incidence of depression in ALS patients in general are disease duration and degree of disability [4,38]. In our admittedly small sample, we did not find such correlations. Nor was there any link between depression and the neuropsychological (similarly, Ref. [35]) and electrophysiological measures (including the N1 and the PN). The N1 amplitude reduction is generally assumed to reflect a reduced arousal level and/or sensory sensitivity underlying a depressive state. Hence, a N1 reduction has been found for depressed patients irrespective of ALS [5,6,48]. Correspondingly, when ALS patients were not depressed, a normal N1 amplitude was observed in an oddball-paradigm [19]. Moreover and irrespective of ALS, the PN was unchanged in young- and middle-aged subjects with mild to moderate depression of different nosology [6,29]. It is therefore unlikely that mood disturbances explain the PN attenuation in our ALS patients.

It has previously been shown that the PN starts later and has a smaller amplitude when both channels are hard to distinguish [20,37]. For this reason, we aimed to reduce the task demands by choosing well distinguishable tone frequencies and target durations for our paradigm. Most remarkably, this enhanced channel discriminability resulted in a difference of the PN, whereas neuropsychological testing did not reveal differences of selective attention, in accordance with earlier studies [2,27,34]. This observation could suggest that our ERP paradigm allows a more subtle detection of the selective attention deficit than neuropsychological testing in non-demented ALS patients.

Lesion and activation studies using neuropsychology [10], PET [12], and fMRI [50] indicate that selective attention is under direction of the frontal lobe [18,40]. Correspondingly, the PN as a measure of auditory selective attention was attenuated in patients with structural lesions of the frontal lobe [28], particularly, of the dorsolateral prefrontal cortex [68]. Therefore, one explanation for the PN attenuation in our ALS patients would be a deficit of frontal lobe function, too. The N1 amplitude reduction among our ALS patients could support this interpretation, because N1 amplitudes have been found lower in patients with lesions of the dorsolateral prefrontal cortex [8].

Our study was not designed to determine the neurochemical mechanism underlying such a presumed frontal lobe deficit. One should, however, remember that the prefrontal cortex receives rich dopaminergic input from both fronto-caudate [10] and mesocortico-mesolimbic afferents [22]. There is now evidence from both pathology [7,24,61] and PET imaging [58] that the nigrostriatal dopaminergic system is compromised in some sporadic and familial ALS patients [31,49]. Remarkably, in Parkinson’s disease itself, the PN has been found reduced [23,57,63]. In our own investigation this reduction was observable only with slow presentation rate. Hence, we argued that this occurred because with slow presentation the unattended stimuli would intrude more readily and subsequently impair the matching process between presented tones and the internal template [63]. Such vulnerability to intrusion could be related to a deficit of the Parkinsonian patients to maintain or switch set [13,65]. It is likely that this interpretation does not entirely explain the findings in our ALS patients, since their PN attenuation was present with both slow and fast presentation rates. Whether this finding points to a basic defect of attention in ALS, remains unexplained with our data.

Remarkably, the PN attenuation of our patients correlated with their motor disability to a surprisingly high degree. It might therefore be speculated that the PN attenuation reflects an impairment of internal executive processes comparable to the ALS-associated disability in external motor acts. Our experiment was not designed to elucidate the chemical or pathological basis of such internal processes. Left aside the already mentioned dopaminergic compromise in some non-demented ALS patients there
are others who show pathoanatomical abnormalities in non-motor limbic and hippocampal areas [44,67]. This non-motor subcortical limbo-thalamo-cortical pathway connecting the hippocampus with the medial prefrontal cortex has been proposed as one of its pathological substrates [25], and attentional deficits are a major feature of the fronto-temporal dementia observed in late ALS patients [42]. It remains therefore to be determined whether the attentional abnormalities derived from our PN results can be related to those anatomical findings; more specifically, whether the cognitive abnormalities found in this study could reflect an early stage of fronto-temporal dementia in ALS.

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