Attenuated Error-Related Potentials in Amyotrophic Lateral Sclerosis with Executive Dysfunctions

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Competing Interests

None of the authors have potential conflicts of interest to be disclosed.

Abstract

Objective: Executive dysfunctions affect up to 50% of the patients with amyotrophic lateral sclerosis (ALS). Executive dysfunctions have been identified as negative prognostic factor and can affect quality of life in patients and their caregivers. Assessment of executive dysfunction may be impeded by the patients' motor impairments. Event-related potentials (ERP) have been proposed as a tool to overcome these assessment difficulties. The error(-related) negativity (Ne/ERN) is an ERP which can be recorded with minimal motor requirements for the patient. **Methods:** We compared response-synchronized ERP amplitudes of 18 ALS patients and 19 healthy controls (HC) obtained on error trials on a flanker task. We also evaluated the relation of Ne/ERN amplitudes to executive functions as assessed by standardized neuropsychological measures. **Results:** While response-synchronized ERP amplitudes were generally unaffected by ALS, we found an ALS-associated relation between Ne/ERN amplitudes and executive functions. ALS patients with poorer executive functioning showed attenuated Ne/ERN amplitudes. **Conclusions:** Our data suggest that Ne/ERN amplitudes reflect ALS-associated impairment of executive functions, potentially due to disturbances in neural networks that involve the anterior cingulate cortex. **Significance:** Assessment of Ne/ERN amplitudes might provide a cost-efficient and non-invasive marker for executive dysfunction in ALS.

Keywords

amyotrophic lateral sclerosis (ALS); event-related potentials (ERP); executive functions; error(-related) negativity (Ne/ERN); cognitive impairment

1 Introduction

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron diseases. It is characterized by progressive degeneration of the upper and lower motor neuron, resulting in muscle paralysis and atrophy. Despite intensive research, curative therapy is still not available. The prognosis is fatal, with a median survival of 2-5 years after disease onset. The incidence in Europe is 2.16 per 100,000 (Logroscino et al., 2010). Different genetic mutations have been associated with the familial form of disease (Robberecht and Philips, 2013), but the etiology of the more common sporadic ALS (90% of cases) remains largely unknown.

ALS has been thought to be restricted to the motor system for a long time, with cognitive impairment being overlooked. However, up to 15% of the patients show manifest frontotemporal dementia (FTD; Phukan et al., 2012; Ringholz et al., 2005), and genetic, clinical, and pathological studies have pointed to strong overlap between FTD and ALS (Devenney et al., 2015; Robberecht and Philips, 2013). Neuropsychological studies have shown less severe cognitive and behavioral deficits also in about 50% of patients without

Abbreviations

ACC = anterior cingulate cortex; ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale Revised; ANOVA = analysis of variance; ECAS = Edinburgh Cognitive and Behavioral ALS Screen; EEG = electroencephalogram / electroencephalography; EP = executive performance; ER = error rate; ERP = event-related potential; FAB = Frontal Assessment Battery; FTD = frontotemporal dementia; HC = healthy control; hEOG = horizontal electrooculogram; KMO = Kaiser-Meyer-Olkin measure; M-WCST = Modified Wisconsin Card Sorting Test; N_c/CRN = correct(-related) negativity; N_e/ERN = error(-related) negativity; PCA = principal component analysis; RT = reaction time; vEOG = vertical electrooculogram

clinically apparent dementia (Lomen-Hoerth et al., 2003; Phukan et al., 2012; Ringholz et al., 2005). Cognitive impairments in ALS are heterogeneous and can affect the patients' language, memory, and executive functions, among others (Beeldman et al., 2016; Goldstein and Abrahams, 2013; Phukan et al., 2007).

Executive functions are higher-level mental processes that control lower-level processes; this ensures that individuals achieve their goals successfully (Friedman and Miyake, 2017; Phukan et al., 2007). Deficits in executive functioning in ALS have been identified as a negative prognostic factor (Elamin et al., 2011). They can also impact the patients' ability to make appropriate decisions—including decisions with regard to treatment options and end-of-life care—and to communicate these (Goldstein and Abrahams, 2013; Phukan et al., 2007). Moreover, executive dysfunctions in ALS have been related to increased burden and lower quality of life in the patients' caregivers, which also threatens the quality of the relationship (often marriage) between patient and caregiver (Chiò et al., 2010). It is therefore essential to adequately capture the cognitive profile of each individual patient to provide optimal support to the patients and their caregivers.

The assessment of cognitive impairments in ALS can be complicated by the patients' physical disabilities (Goldstein and Abrahams, 2013). Event-related potential (ERP; Luck, 2014) measures have been proposed as a tool to examine cognitive functions in ALS (Lange et al., 2016a,d; Raggi et al., 2010; Seer et al., 2015). Due to its excellent temporal resolution, the ERP technique offers the possibility to assess cognitive processes occurring in rapid succession. It is also very well suited to examine executive functions in patients with disorders that affect motor functioning because it can be used with tasks that require only minimal overt action (Lange et al., 2016b,c; Seer et al., 2016, 2017).

One ERP waveform that bears a particularly high potential as a marker of executive dysfunction is the error(-related) negativity (N_e/ERN), which is most likely generated in the anterior (mid-)cingulate cortex (ACC; Falkenstein et al., 1991; Gehring et al., 1993;

Ullsperger et al., 2014a). This waveform is typically observed at fronto-central electrode sites 50-100 ms after the commission of an erroneous action. The N_e/ERN is commonly regarded as a neural correlate of performance monitoring, an aspect of executive functions that refers to surveillance of one's actions in the service of successful goal-directed behavior (Friedman and Miyake, 2017; Ullsperger et al., 2014a,b). Despite its promising potential as an objective marker of executive dysfunctions, the N_e/ERN has hitherto not been investigated in ALS patients. Given its convenient assessment, which can be easily implemented in diagnostic routines, the N_e/ERN amplitude could be ideally suited as a marker for potential future clinical applications: First, its measurement is time- and cost-efficient, as the N_e/ERN can be recorded using conventional EEG systems within several minutes. Good reliability can be achieved based on only eight error trials (Pontifex et al., 2010). Second, the examination is tolerable for the patients because the N_e/ERN is recorded non-invasively from the scalp surface; this is also possible at bedside (Raggi et al., 2010). Third, N_e/ERN elicitation does not require complex motor or verbal responses that may be difficult to obtain from very severely affected ALS patients (Goldstein and Abrahams, 2013).

To pave the way for potential clinical application of N_e/ERN measures, we evaluated N_e/ERN amplitudes in ALS patients and compared them to those of matched healthy control participants. Furthermore, we explored how N_e/ERN amplitudes relate to deficits in executive functions in ALS in an additional post-hoc analysis.

2 Methods

2.1 Participants

Twenty-eight patients fulfilling the revised El Escorial criteria for clinically possible, probable or definite ALS were recruited from Hannover Medical School. Patients were diagnosed by an experienced neurologist in the field of neuromuscular diseases (SP). Patients were not included when they had a history of neurological or psychiatric conditions other than ALS, or when they had manifest FTD.

One patient was not able to complete the task due to insufficient physical strength and was excluded. One patient was excluded due to poor task comprehension. Another eight patients were excluded because less than eight artifact-free error trials were available for these individuals, rendering the evaluation of the N_e/ERN amplitude too unreliable (Pontifex et al., 2010). Most of the patients produced substantially more than eight artifact-free error trials (cf. Supplementary Table S1). The final sample comprised 18 ALS patients (one left-handed). Twelve patients had limb disease onset, whereas six had a bulbar onset. The mean disease duration was 13.50 months ($SD = 12.57$). Clinical status of ALS patients was examined using the revised ALS functional rating scale (ALSFRS-R; Cedarbaum et al., 1999). The mean score on the ALSFRS-R was 34.53 ($SD = 8.21$; range: 15–47). Table 1 displays sociodemographic and clinical characteristics of the participants.

[please insert Table 1 about here]

A group of 29 age-, gender-, and education-matched healthy (i.e., not diagnosed with ALS or any other neurological disease or psychiatric disorder) controls (HC) were recruited by posters distributed throughout the city of Hannover, Germany, and word-of-mouth advertising. One HC participant was excluded after testing due to extremely prolonged motor reaction times ($> 3 SD$ of the sample mean). Another nine HC participants were excluded because less than eight artifact-free error trials were available for these individuals (Pontifex et al., 2010). Most of the control participants produced substantially more than eight artifact-free error trials (cf. Supplementary Table S1). The final HC sample comprised 19 individuals (one left-handed). Sociodemographic details are displayed in Table 1. HC were offered a compensation of 25 €.

All participants had normal or corrected-to-normal vision and intact hearing. The study was reviewed and approved by the local ethics committee (Ethics Committee of Hannover Medical School: vote number 6269). All participants gave written informed consent in accordance with the Declaration of Helsinki.

2.2 Materials and Procedures

Participants completed a computerized version of the Eriksen flanker task (Figure 1; Kopp et al., 1996; Seer et al., 2015). Stimulus material was run by Presentation® (Neurobehavioral Systems, Albany, CA). Stimuli were presented against a gray background on a 24 inch flat screen (Eizo EV2416W, Eizo, Hakusan, Japan). Responses were collected using a Cedrus® response pad (RB 830, Cedrus, San Pedro, CA).

[please insert Figure 1 about here]

Stimuli consisted of three black arrows either pointing to the left or to the right. Arrows were arranged vertically such that the two outer arrows (“flanker”) either pointed to the same (congruent) or to the opposite (incongruent) direction compared to the central arrow (“target”). Incongruent trials are typically associated with longer reaction times (RT) and higher error rates (ER) compared to congruent trials. The spatial distance between flanker and target stimuli was manipulated at two levels (Kopp et al., 1996); this manipulation was not of interest in the present study and will be ignored in the analyses. Neither congruency nor spatial distance affected RT and ER differentially for ALS patients and HC. Targets were presented for 250 ms after an onset delay relative to the flankers that was set to 100 ms. The delay between a response and the next stimulus was set to 800 ms.

Participants were asked to focus on the target to decide whether it pointed to the left or to the right and press a spatially compatible key on the response pad (e.g., a left-hand key press was required whenever the target pointed to the left). For ALS patients who were unable to complete the task bimanually due to severe motor impairment of one hand, a version of the task was used in which the responses were mapped onto the index and middle finger of only one hand. One patient completed the task only using these two fingers of the right hand. Sixteen practice trials were presented to acquaint the participants to the task; then they completed 484 trials, which were presented in four blocks. The average task duration amounted to approximately twelve minutes.

All participants underwent neuropsychological testing prior to completing the flanker task. In the focus of this examination were three well-established standardized assessments of executive functioning: the executive subscore of the revised German version of the Edinburgh Cognitive and Behavioral ALS Screen (ECAS; Abrahams et al., 2014; ALS-specific assessment of executive functions), the Frontal Assessment Battery (FAB; Dubois et al., 2000; Kopp et al., 2013; assessment of frontal lobe functions), and the modified version of the Wisconsin Card Sorting Test (M-WCST; Schretlen, 2010; assessment of cognitive flexibility). Table 1 displays the results that were obtained from these tests.

2.3 Electrophysiological Recording

Continuous EEG was recorded with a BrainAmp amplifier and 30 active Ag-AgCl electrodes (Brain Products, Gilching, Germany) mounted on an actiCap (EASYCAP, Herrsching, Germany) according to the international 10–20 system montage. BrainVision Recorder version 1.20 (Brain Products, Gilching, Germany) was used; the sampling rate was 250 Hz (bandpass: 0.01–70 Hz). Electrode impedance was kept below 10 k Ω . Electrodes were referenced to FCz electrode. To monitor ocular artifacts, vertical (vEOG), and horizontal (hEOG) electrooculogram were recorded with two electrodes positioned at the suborbital ridge and the external ocular canthus of the right eye.

2.4 Data Analysis

Data were analyzed using IBM SPSS 23.0. The significance level was set to .05. Effect sizes were calculated as η_p^2 .

RT and ER were calculated separately for congruent and incongruent trials. RTs were obtained by computing the median response latency on correctly completed trials for each individual. Responses that were registered earlier than 100 ms and later than 2000 ms after target onset were discarded. ERs were calculated as the proportion of erroneous responses (i.e., key press corresponding to the opposite direction of the target). Only trials that were preceded by a correctly completed trial were included in the calculation of RT and ER to rule

out the influence of processes induced by erroneous responding (e.g., post-error slowing; Ullsperger et al., 2014a). Relations between RT and the variables congruency and ALS were analyzed by a mixed ANOVA with Congruency (congruent vs. incongruent) as within-subject factor and Group (ALS vs. HC) as between-subjects factor. Since percentage data are frequently not normally distributed, Group differences with regard to ERs were assessed using independent samples Mann-Whitney U tests (separately for congruent and incongruent trials).

EEG data were analyzed using BrainVision Analyzer 2.0 (Brain Products, Gilching, Germany). Raw data were filtered (high-pass: 0.1 Hz, 24 dB/oct; low-pass: 70 Hz, 24 dB/oct; notch: 50 Hz) and screened for artifacts (voltage step $> 75 \mu\text{V/ms}$; activity $< 0.5 \mu\text{V}/100 \text{ ms}$). An independent component analysis (Jung et al., 2000) was used to correct ocular, muscular and cardiac artifacts. As errors occur rarely on congruent trials, only incongruent trials were used in analyses of response-locked ERPs. Data were segmented into epochs relative to the overt response separately for correct and error trials. The interval for baseline-correction was chosen to approximate a time window preceding stimulus onset [-1,000 ms, -800 ms] (see also Verleger et al., 2013). Remaining artifacts were rejected (voltage difference $> 150 \mu\text{V}/200 \text{ ms}$; amplitude $< -100 \mu\text{V}$ or $> 100 \mu\text{V}$). Only few trials were unsuitable for further evaluation due to excessive artifacts (ALS: correct trials: 1%, error trials: 5%; HC: correct trials: 2%, error trials: 4%). None of the participants who committed at least eight error trials had to be excluded due to excessive artifacts. Data were averaged and re-referenced to a common average reference. The N_e /ERN amplitude and the corresponding negative amplitude on correct trials (“correct(-related) negativity”, N_e /CRN; Falkenstein et al., 2000; Vidal et al., 2000) were determined at FCz electrode as the first negative peak following the overt erroneous and correct response on incongruent trials, respectively, and quantified by subtracting this peak from the peak of the preceding positivity. Supplementary Table S1 displays the average trial numbers for ERP analyses.

Relations between response-synchronized ERP amplitudes and the variables correctness and ALS were analyzed by a mixed ANOVA with Correctness (correct [N_c/CRN] vs. error [N_e/ERN]) as within-subject factor and Group (ALS vs. HC) as between-subjects factor. If response-synchronized ERP amplitudes were altered in ALS patients, this should be reflected in a significant main effect of Group. If potential ALS-related ERP alterations were specific to errors, this should be reflected in a significant Correctness by Group interaction.

2.4.1 The Role of Executive Performance

We further explored how potential disease-related ERP alterations relate to executive functioning in an additional post-hoc analysis. To obtain a measure of executive functioning, we calculated a latent variable using z-standardized values (based on the total sample) of the sum score of the FAB, the number of categories and the number of perseverative errors on the M-WCST, and the sum score of the ECAS executive subscale by subjecting these scores to a principal component analysis (PCA). Latent-variable approaches are particularly suitable to capture the variance shared by multiple measures and are often used in research of executive functions (Friedman and Miyake, 2017). As the M-WCST could not be obtained from one ALS patient and from one HC, these two individuals were excluded from the analyses regarding executive performance. Sampling adequacy was verified by Kaiser-Meyer-Olkin measure ($KMO = .71$). The intercorrelations between the measures of executive functions were sufficiently large for PCA, as indicated by Bartlett's test of sphericity, $\chi^2(6) = 49.73$, $p < .001$ (Field et al., 2012). Only one component had an eigenvalue > 1 , and it explained 63.64% of the variance. This component was used as a general measure of executive performance (EP). The factor loadings of the four input measures on the EP component are displayed in Table 2. EP scores did not significantly differ between ALS patients ($M = -0.02$, $SD = 0.80$) and HC ($M = 0.02$, $SD = 1.18$), $t(33) = -0.11$, $p = .910$, or between ALS patients with bulbar onset ($n = 5$; $M = -0.37$, $SD = 0.63$) and ALS patients with spinal onset ($n = 12$; $M = 0.13$, SD

$= 0.84$), $t(15) = 1.17$, $p = .258$. The distribution of EP scores for ALS patients and HC is displayed in Supplementary Figure S1.

[please insert Table 2 about here]

Both ALS patients and HC were divided into two subgroups as follows: The median of the EP score was calculated separately for ALS patients and HC. Every individual was then either assigned to the below-median (low EP) or to the above-median (high EP) group, depending on the individual score. To evaluate whether the N_e/ERN amplitude is sensitive to EP in ALS, response-locked ERP amplitudes were analyzed by a mixed ANOVA with Correctness (correct [N_e/CRN] vs. error [N_e/ERN]) as within-subject factor, and EP (low vs. high) and Group (ALS vs. HC) as between-subjects factors. If the N_e/ERN amplitude was generally sensitive to EP, N_e/ERN amplitudes, but not N_e/CRN amplitudes, should differ between individuals with low EP and high EP (i.e., an interaction between Correctness and EP should emerge). If the relation between N_e/ERN amplitude and EP was specific to ALS, the three-way interaction between Group, Correctness, and EP should be significant.

Due to the odd number of individuals in the ALS group, the group of patients with low EP comprised $n = 8$ individuals, whereas the group of patients with high EP as well as both EP subgroups in HC each comprised $n = 9$ individuals. The results did not change qualitatively when we repeated the analyses with the ALS patient showing at-median EP assigned to the low-EP group, as in detail below. To further corroborate the robustness of the results, EP was also analyzed as a continuous variable in additional correlation analyses, separately for ALS patients and HC.

3 Results

3.1 Comparison of ALS vs. HC

Incongruent trials were associated with increased RT compared to congruent trials, as indicated by a significant main effect of Congruency (congruent: 406 ms, incongruent: 490 ms, $F(1, 35) = 398.52$, $p < .001$, $\eta_p^2 = .92$) in a Congruency (congruent vs. incongruent) $\times$

Group (ALS vs. HC) ANOVA. No other main effect or interaction was significant (all $F < 3.62$, all $p > .05$). ERs did not significantly differ between ALS patients and HC in congruent (ALS: 1%, HC: 1%, $U = 207.00$, $p = .284$) or incongruent (ALS: 9%, HC: 7%, $U = 123.00$, $p = .150$) trials.

Figure 2 displays the grand average ERP data. Errors in both groups were followed by a negative deflection, the N_e/ERN, which was most pronounced at FCz. A Correctness (correct [N_c/CRN] vs. error [N_e/ERN]) $\times$ Group (ALS vs. HC) ANOVA revealed a significant main effect of Correctness, $F(1, 35) = 78.18$, $p < .001$, $\eta_p^2 = .69$, with smaller amplitudes following correct responses (N_c/CRN: $-3.24 \mu V$) than following errors (N_e/ERN: $-8.79 \mu V$). Amplitudes did not significantly differ between ALS ($-5.94 \mu V$) and HC ($-6.09 \mu V$), $F(1, 35) = 0.04$, $p = .849$, $\eta_p^2 < .01$, and the Correctness $\times$ Group interaction was not significant, $F(1, 35) = 2.12$, $p = .155$, $\eta_p^2 = .06$ (ALS: N_c/CRN: $-3.62 \mu V$, N_e/ERN: $-8.25 \mu V$; HC: N_c/CRN: $-2.86 \mu V$, N_e/ERN: $-9.32 \mu V$). Taken together, behavioral performance and N_e/ERN amplitudes were not generally altered in ALS patients in comparison to HC.

[please insert Figure 2 about here]

3.2 The Role of Executive Performance

A Correctness (correct [N_c/CRN] vs. error [N_e/ERN]) $\times$ EP (low vs. high) $\times$ Group (ALS vs. HC) ANOVA revealed a trend toward significance for the interaction between EP and Group, $F(1, 31) = 3.89$, $p = .058$, $\eta_p^2 = .11$. Crucially, the three-way interaction of Correctness, EP, and Group proved significant, $F(1, 31) = 4.81$, $p = .036$, $\eta_p^2 = .13$, indicating that the sensitivity of N_e/ERN amplitudes to EP differed between ALS patients and HC.

Follow-up analyses (Figure 3) were calculated as EP (low vs. high) $\times$ Group (ALS vs. HC) ANOVAs separately for correct (N_c/CRN) and error (N_e/ERN) trials. These analyses revealed a significant interaction of EP and Group on error trials, $F(1, 31) = 5.33$, $p = .028$, $\eta_p^2 = .15$. In ALS patients, N_e/ERN amplitudes were significantly smaller in low executive performers ($-5.69 \mu V$) than in high executive performers ($-11.14 \mu V$), $t(15) = 2.91$, $p = .011$.

(see Supplementary Figure S2). ALS patients with low executive performance also had attenuated N_e/ERN amplitudes compared to HC with low executive performance, $t(15) = 2.79$, $p = .014$. In contrast, N_e/ERN amplitudes did not differ between the two EP subgroups in HC (low: $-9.62 \mu\text{V}$, high: $-9.49 \mu\text{V}$), $t(16) = -.082$, $p = .935$. For N_e/CRN amplitudes, the interaction of EP and Group was not significant, $F(1, 31) = 0.15$, $p = .702$, $\eta_p^2 = .01$.

[please insert Figure 3 about here]

When the ALS patient with the at-median performance was assigned to the low-EP group (rather than to the high-EP group), the results were similar: The three-way interaction of Correctness $\times$ EP $\times$ Group was significant, $F(1, 31) = 6.33$, $p = .017$, $\eta_p^2 = .17$. The EP $\times$ Group interaction for N_e/ERN amplitudes was also significant, $F(1, 31) = 7.03$, $p = .013$, $\eta_p^2 = .19$. N_e/ERN amplitudes were smaller in low performing ALS patients ($-5.74 \mu\text{V}$) than in high performing ALS patients ($-11.77 \mu\text{V}$), $t(15) = 3.46$, $p = .004$.

To further corroborate the robustness of the results, we also examined the relation between EP and response-locked ERP amplitudes in a correlation analysis, where EP was treated as a continuous rather than as a dichotomous variable. While there was no significant correlation between N_e/ERN amplitude and EP in HC, $r = -.06$, $p = .815$, EP correlated with N_e/ERN amplitude in the ALS patients, $r = -.52$, $p = .034$ (see Figure 4). The correlation coefficients did not significantly differ between ALS patients and HC, $z = -1.39$, $p = .165$. N_e/CRN amplitudes did not significantly correlate with EP neither in ALS ($r = -.26$, $p = .320$) nor in HC ($r = .13$, $p = .616$).

[please insert Figure 4 about here]

4 Discussion

We compared ERP amplitudes elicited by behavioral errors (N_e/ERN) between ALS patients and matched HC. There were no ALS-related abnormalities in behavioral performance or N_e/ERN amplitude. In an additional exploratory analysis, we found N_e/ERN amplitudes to be sensitive to a composite measure of executive functioning in ALS patients.

ALS patients with poorer executive functions showed significantly attenuated N_e/ERN amplitudes compared to ALS patients with better executive functions and compared to HC.

The comparison of response-locked (N_e/CRN, N_e/ERN) ERP amplitudes between ALS patients and HC did not reveal significant differences between these two groups. Of course, the absence of a significant result is difficult to interpret and cannot be taken to indicate the actual absence of a true effect. However, the results presented here do not show large alterations in N_e/ERN amplitudes in association with ALS in general. In addition, the fact that the patients examined here were relatively mildly affected (see below for further discussion) could have constituted another factor contributing to the minimization of overall group differences.

Rather than generally comparing ALS patients and a control sample, it appears more promising to analyze the relation between these ERPs and more specific cognitive functions (such as executive performance) in ALS. An additional exploratory analysis of our data suggested that N_e/ERN amplitudes appear to be related to executive dysfunctions in ALS. Given that the N_e/ERN is probably generated in the ACC, this pattern of results might indicate alterations in the ACC (or in related neural structures) in ALS patients who show signs of executive dysfunctions in conventional neuropsychological assessment. This interpretation is supported by a variety of studies demonstrating grey and white matter atrophy as well as neuropathological and functional changes in the ACC in ALS (Abrahams et al., 1996; Filippini et al., 2010; Li et al., 2012; Mohammadi et al., 2015; Pettit et al., 2013; Strong, 2009; Tsermentseli et al., 2012; Turner et al., 2012; Wilson et al., 2001). Neuropathological, structural, and functional ACC changes appear to be particularly prominent in cognitively impaired compared to cognitively unimpaired ALS patients (Abrahams et al., 1996; Tsermentseli et al., 2012; Wilson et al., 2001), suggesting a relation between disturbed ACC function and the disruption of executive functioning in ALS.

It remains to be investigated in neuropathological and imaging studies whether and how the relation between N_e/ERN amplitudes and executive dysfunctions in ALS is associated with ACC alterations. Notwithstanding, the present data give a first indication that N_e/ERN amplitude could be a cost-efficient, non-invasive tool to assess executive functioning in ALS when standard neuropsychological assessment is hampered by the patients' physical disabilities: the requirements for the patients' motor abilities are minimal when measuring the N_e/ERN. Here, we evaluated the N_e/ERN based on errors that were committed by pressing a key using the index fingers of both hands (or alternatively, the index and middle finger of one hand in the case of one patient who could not use both hands due to motor impairments). However, the N_e/ERN does not require the patient to respond by a movement of the hand, but can also be elicited by foot or eye movements (Ullsperger et al., 2014a). Another advantage of the N_e/ERN as a measure of executive functioning is that it can be reliably measured based on relatively few error trials (Pontifex et al., 2010). Errors can be provoked in simple paradigms where the patients are asked to respond to stimuli by pressing one of two keys (e.g., the flanker task). Increasing the task difficulty, e.g., by introducing time pressure, can help to induce sufficient numbers of errors in relatively short periods of time. This would also prevent the exclusion of individuals with error rates that are too low for the meaningful analysis of N_e/ERN amplitudes, as necessary in the present study. The independence of response modality in combination with the simple recording apparatus allows for N_e/ERN-based assessments of executive dysfunction to be performed at bedside, especially for patients who suffer from severe physical disabilities.

The patient sample in the present study had a relatively short disease duration (about 14 months) and was comparably mildly affected (ALSFRS-R score of about 35). Nevertheless, a relation between executive performance and N_e/ERN amplitudes could be detected in these patients. Hence, alterations of N_e/ERN amplitudes might possibly constitute

an early indicator of cognitive impairment in ALS, which remains to be investigated in longitudinal studies.

In contrast to the substantial correlation of executive functions and N_e/ERN amplitudes in patients with ALS, we did not find a significant relation between these variables in HC. This pattern is similar to the data presented by Kim and colleagues (2006), who found a correlation between N_e/ERN and executive functions in a group of patients with schizophrenia, but not in a healthy control sample. Taken together, our data and those of Kim and colleagues suggest that the link between N_e/ERN and executive functions might be particularly strong in clinical populations. This interpretation is also supported by the significant three-way interaction between correctness, group, and executive performance, which suggests differential relations between error-related ERPs and executive performance in ALS and HC. Our data do not, however, allow for the conclusion that N_e/ERN amplitudes are unrelated to executive functions in healthy individuals. First, the correlation coefficients for the association between N_e/ERN and executive performance did not significantly differ between the groups. Hence, a conclusion with regard to the specificity of the relation between these two measures cannot be drawn with certainty. Second, Larson and Clayson (2011) have reported a moderate association (i.e., $r = -.24$ to $-.27$) between some executive functions (but not other cognitive functions, such as memory or verbal fluency) and N_e/ERN amplitudes in a large sample of healthy young adults. The factors moderating the strength of the association between N_e/ERN amplitudes and executive performance need to be examined in future studies.

When interpreting these data, one should take into account the limitations associated with the exploratory character of the analyses related to executive performance. In particular, given the small number of observations, the statistical power was relatively low, which likely lead to an overestimation of the true effect's size (Gelman and Carlin, 2014). To determine

the robustness of the findings reported here, and to get a more realistic estimate of the effect size, replication in larger samples is warranted.

In summary, our data reveal no ALS-related abnormalities in N_e/ERN amplitudes. They do, however, point to a sensitivity of N_e/ERN amplitudes for executive functioning in ALS. This suggests that neural networks involved in the generation of the N_e/ERN, possibly those involving the ACC, might be related to the development of executive dysfunctions in ALS. N_e/ERN amplitudes could bear a promising potential as cost-efficient, non-invasive ALS-specific markers of executive dysfunction, even in severely affected ALS patients. This study demonstrates the potential utility of ERP measurement for the assessment of cognitive impairment in ALS.

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Figure 1 The Eriksen flanker task. On every trial, three vertically arranged arrows are presented. Participants are instructed to ignore the distracting outer arrows (“flanker”), and to press a key that is spatially compatible to the direction of the central arrow (“target”). On congruent trials (a), flankers point in the same direction as the target, whereas on incongruent trials (b), flankers point in the opposite direction compared to the target. Errors (c) mostly occur on incongruent trials.

Figure 2 Response-synchronized grand average ERP waveforms (with 95% confidence intervals) for ALS patients (red) and HC (blue) against a baseline of -1000 to -800 ms before the overt response. Solid lines indicate waveforms elicited by errors (N_e/ERN), dashed lines indicate waveforms elicited by correct responses (N_c/CRN). Fronto-central N_e/ERN amplitudes do not differ significantly between ALS patients and HC.

Figure 3 Mean N_c/CRN and N_c/ERN amplitudes (error bars indicate standard errors) observed in individuals with low and high executive performance, separately for ALS patients and HC. N_c/CRN amplitudes are not sensitive to executive performance in ALS patients and HC. However, N_c/ERN amplitudes vary as a function of executive performance in ALS patients. Note that these values indicate average peak-to-peak differences and are therefore more negative than the most negative peaks displayed in Figure 2.

Figure 4 Relationship between executive performance (EP) factor score (arbitrary units) and N/ERN amplitudes for ALS patients (black circles) and HC (white circles). Regression lines indicate a negative correlation between executive performance and N/ERN amplitudes in ALS (solid line), but not in HC (dotted line).

Table 1.

Sociodemographic and clinical characteristics of ALS patients (ALS) and healthy control participants (HC) included in the final analysis of N/ERN amplitudes.

	max	Mean (Standard Deviation)		<i>p</i>
		ALS (<i>N</i> = 18)	HC (<i>N</i> = 19)	
gender		11 male / 7 female	13 male / 6 female	.642
age [years]		63.56 (11.34)	61.95 (13.73)	.701
education [years]		13.44 (2.62)	14.87 (3.88)	.202
ECAS total	136	106.83 (13.35)	108.63 (15.76)	.711
ECAS ALS-specific	100	78.22 (11.07)	80.11 (12.14)	.626
language	28	25.50 (2.75)	26.11 (2.42)	.482
fluency	24	17.67 (5.41)	18.95 (3.73)	.406
executive	48	35.06 (6.18)	35.05 (7.86)	.999
ECAS ALS-non-specific	36	28.61 (4.41)	28.53 (4.51)	.954
memory	24	16.89 (4.31)	16.89 (3.76)	.997
visuospatial	12	11.72 (0.46)	11.63 (1.38)	.793
FAB	18	15.89 (1.68)	15.89 (2.21)	.993
M-WCST				
number of categories	7	3.47 (1.77) ^a	3.72 (1.71) ^b	.672
perseverative errors	47	4.71 (3.35) ^a	5.28 (5.22) ^b	.704

Note. max = maximum value of the respective measure; ECAS = Edinburgh Cognitive and Behavioral ALS Screen (Abrahams et al., 2014); FAB = Frontal Assessment Battery (Dubois et al., 2000; Kopp et al., 2013); M-WCST = Modified Wisconsin Card Sorting Test (Schretlen, 2010)

^abased on *n* = 17

^bbased on *n* = 18

Table 2.

Factor loadings of the input measures on the executive performance (EP) component

	EP
FAB (sum score)	.68
M-WCST (number of categories)	.83
M-WCST (number of perseverative errors)	-.87
ECAS (executive functioning subscale)	.81

Note. FAB = Frontal Assessment Battery (Dubois et al., 2000; Kopp et al., 2013); M-WCST = Modified Wisconsin Card Sorting Test (Schretlen, 2010); ECAS = Edinburgh Cognitive and Behavioral ALS Screen (Abrahams et al., 2014)

Attenuated Error-Related Potentials in Amyotrophic Lateral Sclerosis
with Executive Dysfunctions

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Supplementary Material

Supplementary Table S1.

Means (M), standard deviations (SD) and range (min, max) of the numbers of trials included in the analyses of response-locked ERPs (N/CRN, N/ERN) for patients with amyotrophic lateral sclerosis (ALS) and healthy controls (HC).

	ALS (N = 18)				HC (N = 19)			
	<i>M</i>	<i>SD</i>	min	max	<i>M</i>	<i>SD</i>	min	max
N/CRN	217.94	10.00	195	232	220.32	11.78	194	232
N/ERN	19.83	9.53	8	46	17.37	10.99	8	43

Supplementary Figure S1. Frequency distributions of the executive performance (EP) principal component scores separately for patients with amyotrophic lateral sclerosis (ALS; black) and healthy control participants (HC; white). The histogram was created by dividing the data into nine equally large bins (range: -3.5 – 3.5).

Supplementary Figure S2. Response-synchronized grand average ERP waveforms (with 95% confidence intervals) for patients with amyotrophic lateral sclerosis (ALS; left) and healthy control participants (HC; right) against a baseline of -1000 to -800 ms before the overt response, separately for individuals with low (red) and high (blue) executive performance (EP). Solid lines indicate waveforms elicited by errors (N/ERN), dashed lines indicate waveforms elicited by correct responses (N/CRN). N/ERN amplitudes appear to be sensitive to EP in ALS.