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Attenuated error-related potentials in amyotrophic lateral sclerosis with executive dysfunctions

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HIGHLIGHTS

- We studied error monitoring in ALS patients and healthy controls (HC) using event related potential recordings.
- Error-related negativities (N_e/ERN) did not generally differ between ALS and HC.
- N_e/ERN amplitudes were associated with executive performance in ALS.

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 (N_e/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 between N_e/ERN amplitudes and 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 N_e/ERN amplitudes and executive functions. ALS patients with poorer executive functioning showed attenuated N_e/ERN amplitudes.
Conclusions: Our data suggest that N_e/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 N_e/ERN amplitudes might provide a cost-efficient and non-invasive marker for executive dysfunction in ALS.

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

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.

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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 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, 2016d; 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, 2016c; 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, 2014b). 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; but see also Fischer et al., in press). 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.

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 (Fig. 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 EV2416 W, Eizo, Hakusan, Japan). Responses were collected using a Cedrus® response pad (RB 830, Cedrus, San Pedro, CA).

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