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Neural correlates of cognitive set shifting in amyotrophic lateral sclerosis

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HIGHLIGHTS

- Event-related potentials reveal set-shifting alterations in amyotrophic lateral sclerosis (ALS).
- Shift-related cortical activity is also attenuated in patients without overt cognitive impairment.
- Event-related potentials are a valuable tool for the detection of subtle cognitive changes in ALS.

ABSTRACT

Objective: Amyotrophic lateral sclerosis (ALS) has been associated with executive dysfunction, particularly in the domain of cognitive set shifting. In a recent event-related potential (ERP) study, shifting-related cortical activity on a complex set-shifting paradigm was found to be attenuated in patients with ALS. Here, we investigated whether this ERP change could also be observed in a simplified set-shifting task adapted for potential clinical use, and in ALS patients without overt cognitive impairment.
Methods: Twenty-six patients and 28 matched healthy controls (HC) completed a set-shifting paradigm involving two task rules and explicit task cues. Cue-locked ERPs were analyzed.
Results: ALS patients and HC did not differ in response latency or accuracy. In HC, cues that required shifting task rules elicited more positive parietal ERP waveforms than cues that signaled a rule repetition. This shifting-related amplitude modulation was absent in patients with ALS. The attenuation of ERP activity in ALS patients remained significant when participants with possible cognitive impairment were excluded.
Conclusions: Electrophysiological measures can detect ALS-related changes in the neural substrates of set shifting even when these changes do not become apparent in neuropsychological assessment.
Significance: These findings illustrate the potential utility of ERPs as indicators of cognitive change in ALS.

1. Introduction

In 1874, Jean-Marc Charcot coined the term amyotrophic lateral sclerosis (ALS) to denote a clinical combination of muscular atrophy and contractures that can be linked to the loss of upper and lower motor neurons (Rowland and Shneider, 2001). Almost a century later, it became apparent that nerve cell degeneration in ALS is not restricted to motor neurons, but also extends to involve extramotor areas of the cerebral cortex (Smith, 1960). These early findings from post-mortem studies converge with recent advances in neuroimaging, neurogenetics, and neuropathology in demonstrating that ALS is, in fact, a multisystem neurodegenerative disorder (Braak et al., 2013; Brettschneider et al., 2015; Robberecht and Philips, 2013; Sheng et al., 2015; Turner et al., 2012). The widespread pattern of cerebral neurodegeneration in ALS has been proposed to account for the cognitive alterations that can be observed in a subset of ALS patients (Abrahams et al., 2005; Pettit et al., 2013; Tsermentseli et al., 2012). One of the best documented cognitive symptoms in ALS is impairment in executive functioning (Abrahams et al., 2000; Beeldman et al., 2015; Goldstein and Abrahams, 2013; Lomen-Hoerth et al., 2003; Phukan et al., 2007; Zalonis et al., 2012). Executive functions refer to a set of high-level cognitive processes that allow for the pursuit of complex goals by exerting top-down control on lower-level processes (Diamond, 2013; Elliott, 2003; Friedman and Miyake, 2016). Executive dysfunction has been shown to affect up to 50% of ALS patients (Phukan et al., 2012; Ringholz et al., 2005) and to be associated with both shortened survival of ALS patients and increased caregivers' burden (Burke et al., 2015; Chio et al., 2010; Elamin et al., 2011, 2015; Montuschi et al., 2015; Olney et al., 2005). Against this background, the present study aimed at contributing

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to an improved understanding of ALS-related cognitive alterations as well as to the search for objective and clinically applicable biomarkers of executive dysfunction in ALS.

Executive functions in ALS are often investigated using the Wisconsin Card Sorting Test (WCST, Berg, 1948; Grant and Berg, 1948; Heaton et al., 1993). On the WCST, examinees have to sort cards in accordance with one of three viable task rules. After a number of trials, the valid task rule changes. Examinees are then required to identify the new task rule by evaluating the experimenter's feedback. When having found the correct new rule examinees have to maintain it until they are informed that the rule has changed again. Two recent meta-analyses across neuropsychological studies have found significantly impaired WCST performance in ALS, with the difference between ALS patients and healthy controls being medium in size (i.e., around $d = 0.5$) (Beeldman et al., 2015; Lange et al., 2016a). However, these meta-analyses are not informative with regard to the precise cognitive and neural mechanisms underlying WCST performance deficits in ALS.

The WCST is often regarded as a prototypical test of set shifting (or cognitive flexibility) (e.g., Monchi et al., 2004; Phukan et al., 2007), a cognitive ability that has been demonstrated to constitute one of the basic factors of executive functioning (Miyake et al., 2000). Closer inspection of its task structure reveals, however, that the WCST is not a pure set-shifting test, but rather requests multiple additional cognitive processes such as working memory, category learning, and rule inference (Buchsbaum et al., 2005; Dehaene and Changeux, 1991; Lange et al., 2016b,c,d; Ridderinkhof et al., 2002). This implies that WCST performance deficits in ALS cannot unequivocally be attributed to an ALS-related set-shifting impairment.

In the present study, we investigated whether ALS relates to deficits on a simplified set-shifting paradigm associated with substantially reduced demands on working memory, category learning, and rule inference (Kopp et al., 2006). If set-shifting deficits contributed to the repeatedly observed pattern of impaired WCST performance in ALS, they should also become apparent in this simplified paradigm.

We combined our analysis of set-shifting performance in ALS with the recording of event-related potentials (ERPs). Recent years have witnessed an increasing interest in the analysis of ERPs for the study of cognition in ALS (Amato et al., 2013; Hammer et al., 2011; Mannarelli et al., 2014; Raggi et al., 2010; Seer et al., 2015; Silvoni et al., 2016; Thorns et al., 2010; Volpato et al., 2010, 2016; Zaehle et al., 2013). This interest appears to be fueled by a number of methodological advantages associated with the ERP technique. First, due to its excellent temporal resolution, the ERP technique allows dissociating different stages of information processing that are likely to be confounded in the analysis of behavioral performance data (Duncan et al., 2009). Second, in contrast to most neuropsychological tests, ERP indicators of cognitive processes can be obtained without requiring overt movement on the part of the participant, rendering them particularly attractive for use in ALS patients where motor symptoms might distort the results of neuropsychological testing (Goldstein and Abrahams, 2013). In addition, this property of the ERP technique offers promising opportunities for the design of brain-computer interfaces that might provide locked-in ALS patients with an alternative way to communicate (Poletti et al., 2016; Sellers and Donchin, 2006). Finally, ERPs might provide objective and clinically applicable biomarkers of cognitive state during disease progression (Solís-Vivanco et al., 2015).

In our previous ERP study using a computerized variant of the WCST with visual feedback cues, we found a reduction of shifting-related ERP activity in patients with ALS (Lange et al., 2016a). In comparison to HC, ALS patients showed attenuated amplitudes of the posterior switch positivity (PSP). The PSP refers to a difference potential that is obtained by contrasting the ERP waveforms elicited by *switch cues* (i.e., those cues that signalize that the rule has to be changed) and *repeat cues* (i.e., those cues that signalize that the rule has to be maintained). Switch cues are typically associated with a more prominent late positivity over parietal electrodes than repeat cues (Barceló et al., 2002; Karayanidis et al., 2010; Karayanidis and Jamadar, 2014; Kopp and Lange, 2013; Kopp et al., 2014; Lange et al., 2015; Tarantino et al., 2016). The PSP likely reflects the activation of fronto-parietal brain networks (Karayanidis et al., 2010). There is widespread consensus that the PSP can serve as a neurophysiological index of set-shifting processes (Jamadar et al., 2010; Karayanidis et al., 2010; Lavric et al., 2008).

The functional significance of PSP amplitude attenuation in ALS is illustrated by our observation that PSP amplitudes were related to patients' performance on the WCST (Lange et al., 2016a). This finding converged with the results of a functional magnetic resonance imaging (fMRI) study that found a correlation between connectivity in the right fronto-parietal cortical network (i.e., the likely generator of the PSP) and WCST performance in ALS patients (Agosta et al., 2013). Hence, the PSP might serve as an indicator of the integrity of fronto-parietal networks required for executive functioning in general or set-shifting processes in particular.

We investigated whether the ALS-related attenuation of PSP amplitude can be replicated using a simplified set-shifting paradigm. If PSP amplitudes were only attenuated in ALS patients when a particular task (e.g., the computerized WCST) is used, this ERP change would be unlikely to reflect a general shifting-related impairment in ALS. In contrast, evidence for reduced PSP amplitudes in ALS in multiple set-shifting paradigms would substantially support the generalizability of this finding.

In addition, our previous study was conducted on a relatively unselected sample of ALS patients: some patients performed well on all neuropsychological tests and the computerized WCST, while others showed overt deficits in executive functioning. The present study included a sufficient number of cognitively unimpaired ALS patients to investigate whether PSP amplitudes are also attenuated in ALS patients in the absence of any overt signs of cognitive impairment.

In sum, our previous finding of impaired WCST performance and attenuated PSP amplitudes in patients with ALS raised a number of research questions that we aimed to address with the present study. First, we examined whether there is a general set-shifting deficit in ALS that also manifests in performance decrements on a simplified set-shifting paradigm associated with substantially reduced demands on working memory, category learning, and rule inference. In addition, our study design allowed testing if the observed attenuation of PSP amplitudes in ALS can be replicated using this simplified set-shifting paradigm. Finally, we investigated whether the amplitude of the PSP is also attenuated in ALS patients who do not show any overt signs of cognitive impairment.

2. Methods

2.1. Participants

Twenty-six patients diagnosed with ALS (11 females, 15 males; one left-handed, 25 right-handed) were recruited from the Department of Neurology of Hannover Medical School between April and July 2015. All patients were diagnosed with ALS according to the revised El Escorial Criteria (Brooks et al., 2000; four patients with definite ALS, 15 patients with probable ALS, and seven patients with possible ALS). Ten patients had bulbar and 16 patients had spinal disease onset. Mean disease duration was 11.96 months