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Movement initiation and inhibition are impaired in amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) features central and peripheral paresis owing to the degeneration of upper and lower motor neurons. Here, we asked whether motor preparation and inhibition are also affected. Thirteen ALS patients and thirteen matched controls participated in an event-related brain potentials (ERP) experiment in which a cue stimulus indicated whether the following target stimulus was to be responded to by the left or the right hand by a speeded button press. In 25% of the trials a stop-signal followed the target stimulus (onset asynchrony 150 ms) indicating that participants had to abort the already initiated motor response. ERPs indicated deficits of the ALS patients in the preparation and inhibition of motor responses: The lateralized readiness potential indicating motor preparation had a grossly reduced amplitude. A right frontal negative component following about 200 ms after the stop-signal and known to indicate inhibitory processes was diminished in amplitude and prolonged in latency in ALS. Finally, a later negative component associated with error processing was also reduced in amplitude in ALS. These electrophysiological changes were accompanied by behavioral deficits in the patient group (less efficient stopping of movements, no reaction time adaptation after stop trials). In conclusion, ALS patients showed deficits in both, movement initiation and inhibition, with the latter associated with prefrontal dysfunction.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative disorder of the nervous system of still unknown cause with muscular atrophy, spasticity and bulbar signs as its clinical hallmarks. These can be attributed to a loss of the upper and lower motor neurons. Pathological (Brownell et al., 1970; Maekawa et al., 2004), neuropsychological (Abrahams et al., 1997; Frank et al., 1997; Phukan et al., 2007) as well as neuroimaging results (Abrahams et al., 1996; Hatazawa et al., 1988; Ludolph et al., 1992; Mohammadi et al., 2009; Schreiber et al., 2005) suggest, however, that the disease process involves additional parts of the nervous system. In particular, abnormalities in regional cerebral blood flow (rCBF) have been observed in lateral and medial premotor areas and the supplementary motor area in a PET activation study addressing executive functions (Abrahams et al., 1996). Reduced rCBF in the lateral premotor cortex (area 6) and the supplementary motor area was also found in resting state scans using PET (Kew et al., 1993a,b) and more recently our group found a reduction of activity in the premotor area employing independent component analysis of resting state fMRI (Mohammadi et al., 2009).

The involvement of the premotor cortex and the supplemental motor area (SMA) suggests that ALS might affect movement initiation, coordination, and inhibition, but evidence for this is scarce. The current study set out to fill this gap by recording event-related brain potentials (ERPs) in a forewarned choice-reaction time task with left and right hand responses, thus allowing to assess the preparation of movements by the recording of lateralized readiness potentials (Hackley and Miller, 1995; Hackley and Valle-Inclan, 2003). Moreover, we introduced a stop-manipulation, requiring patients to inhibit an already initiated movement (De Jong et al., 1990; Logan and Cowan, 1984) in order to assess movement inhibition.

With regard to movement initiation and preparation in ALS, one previous study has investigated the readiness potential (or "Bereitschaftspotential", RP) in 16 ALS patients and found no significant differences in the RP amplitude between ALS patients and matched controls (Westphal et al., 1998). Only when a subgroup of 7 patients with pronounced spasticity was formed, significantly lower amplitudes of the readiness potential were seen.

To our knowledge no previous event-related potential study has focused on inhibitory processes in ALS. One way to investigate processes that underlie movement inhibition is the so-called stop-paradigm (Logan and Cowan, 1984) that we used in the current study. In this type of paradigm a stimulus requiring a choice-reaction is administered, which is infrequently followed by a stop-signal requiring the participant to stop the already initiated response.

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Normal participants need approximately 200 ms to stop their responses irrespective of the response modality (button presses, verbal report, or eye movements; Curtis et al., 2005; Logan and Cowan, 1984).

Several functional imaging studies in normal participants suggest the right medial and inferior prefrontal cortex to be important for successful inhibition in the stop-paradigm (Garavan et al., 2006, 1999; Marco-Pallares et al., 2008; Rubia et al., 2001). This is further corroborated by the fact that the performance of patients with lesions in these brain areas is severely impaired in the stop-paradigm (Aron et al., 2003). A recent magnetoencephalographic experiment showed that following the stop-signal activation of the motor cortex is reduced in the successful relative the unsuccessful stop trials (Boehler et al., 2009).

Several event-related potential (ERP) studies have used variants of the stop-paradigm (Kok et al., 2004; Krämer et al., 2007; Ramautar et al., 2004, 2006; Van Boxtel et al., 2001). Assessment of ERPs in the stop paradigm can be difficult because components related to the target (go) stimulus and components following the stop-signal overlap (Ramautar et al., 2004). Several findings are of importance for the present study: Kok et al. (2004) and Ramautar et al. (2004, 2006) demonstrated a mediofrontal negativity with a latency of 250–300 ms (relative to the stop-signal) which was enhanced for unsuccessful compared to successful stop trials. This effect was interpreted as reflecting the processing of error information in the unsuccessful stop trials. Pliszka et al. (2000) and Schmajuk et al. (2006) identified an earlier negativity with a right frontal distribution that did not differ between successful and unsuccessful stop-trials but showed a marked difference between normal children and children with attention-deficit hyperactivity disorder. This effect was interpreted as a correlate of response inhibition. Finally, a late positive component (P3) has also been observed in stop-trials which is usually more prominent in successful stop trials (Kok et al., 2004; Ramautar et al., 2004, 2006).

In the present study we tackled the question, whether the known involvement of the premotor cortex and SMA in ALS (Kew et al., 1993a,b; Mohammadi et al., 2009) leads to qualitative and quantitative changes in these aspects of motor behaviour by assessing brain potential components related to the initiation (LRP) and abortion of movements.

Methods

Patients and control participants

Thirteen patients with definite or probable ALS according to the revised El Escorial criteria (Brooks et al., 2000) were recruited (age 40–69 years; mean age 55.2 years; 5 women; duration of disease 1–10 years; median duration 2.8 years; ambulation index 2–8; mean ambulation index 4.9). The one patient with 10 years of disease duration was clearly an outlier (without this patient duration 1–5 years). In spite of the long duration of the disease, this patient was able to perform the button press task, as were the other participants. All but one patient received treatment with Riluzole® (2×50 mg/day). None of the patients required assisted ventilation.

Control subjects (n = 13) were matched closely for age, sex, handedness and education and were recruited from various sources (age 36–68 years, mean age 56.8 years, 5 women). All control subjects were free of neurological diseases. Vision was normal or corrected to normal for both subject groups. All subjects gave their informed consent and the study was approved by the local ethics committee.

Participants underwent a comprehensive neuropsychological test battery including several subtests of the German version of the Wechsler adult intelligence scale (WAIS), the recurring figures test (Sturm and Willmes, 1999), the recurring words test (Sturm and Willmes, 1999), a version of the stroop interference task (Lezak et al., 2004), the d2 visual attention test (Brickenkamp and Zillmer, 1998) and the "controlled oral word association" word fluency task (Lezak et al., 2004). ALS patients had slight but significant impairments in word fluency, a function that is attributed to the frontal lobe, as well as difficulties with verbal and figurative recognition memory. Importantly, no general intellectual decline was seen and none of the patients had signs of frontotemporal dementia.

General procedure

Subjects were seated in a comfortable chair with a headrest and were instructed to relax. Training trials were administered to ensure that subjects understood the task. Before each experimental run, they were reminded to minimize blinking and ocular movements as much as possible and were required to fixate a dot in the center of the screen during the experiment. Whenever eye-movements were detected through monitoring of the electro-oculogram (see below), participants received verbal feedback after the respective experimental run.

Paradigm

A left or right pointing arrow was presented for 100 ms at the center of the screen. It indicated the hand of response. After an interval of 500 to 900 ms (randomly chosen with uniform distribution) the arrow was followed by a white square of 3 by 3 cm in size and 60 ms duration. In 25% of the trials the white square was followed after 150 ms by a red square with a duration of 60 ms. The subjects were instructed to press a button as quickly as possible in response to the white square ("go" stimulus) with the left or right index finger (according to the direction of the arrow) but to withhold the response when the white square was succeeded by the red square ("stop" stimulus). Some 900 to 1400 ms after a white square the next trail began (interval randomly chosen with rectangular distribution). After initial explanations the subjects were trained such that they made less than 15% errors on go-trials (misses or false alarms as classified later). Subsequently, the subjects underwent a total of 1080 trials which were administered in 3 experimental blocks. The viewing distance was 90 cm.

EEG recording and analysis

The EEG was recorded from all 19 electrodes of the International 10/20 system referenced to an electrode located on the right mastoid. Horizontal eye movements were monitored with electrodes located on the outer ocular canthi which were referenced to one another and vertical eye movements were detected through an electrode located below the right eye which was referenced to the electrode on the right outer ocular canthus. All channels were amplified (bandpass filter between 0.01 and 100 Hz), digitized at a rate of 256 Hz and stored on a harddisk.

After artifact rejection for exessive eye movements (±75 μV) or amplifier blocking ERPs were separately averaged for the different stimulus/response categories for epochs of 1024 ms including a 100-ms prestimulus baseline.

The lateral readiness potential was assessed at C3 and C4 electrode locations, where the amplitude of the readiness potential is maximal. The LRP was computed by a double subtraction as shown in the following equation:

$$\mathrm{LRP} = \mathrm{left\,hand}\,(\mathrm{C4} - \mathrm{C3}) - \mathrm{right\,hand}(\mathrm{C4} - \mathrm{C3})$$

Left and right hands refer to the expected correct hand and (C4 − C3) is the difference in electrical potential between these electrodes (Gratton et al., 1988). The resulting LRP component is of negative polarity, if the correct response is prepared.

For statistical analysis, mean amplitude measures were obtained and entered into ANOVA-statistics with the Huynh–Feldt epsilon

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