Neuroscience Letters 543 (2013) 172–176

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Altered cortical communication in amyotrophic lateral sclerosis

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HIGHLIGHTS

- We compare cortical communication between individuals with and without ALS.
- We measure directed functional connectivity between frontal and parietal regions.
- Feedback connectivity is not significantly different between groups.
- Feedforward connectivity is significantly higher in individuals with ALS.

ARTICLE INFO

Article history:
Received 19 February 2013
Received in revised form 16 March 2013
Accepted 28 March 2013

Keywords:
Amyotrophic lateral sclerosis
Directed functional connectivity
Symbolic transfer entropy
Frontoparietal connectivity
Recurrent processing
Electroencephalography

ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a disorder associated primarily with the degeneration of the motor system. More recently, functional connectivity studies have demonstrated potentially adaptive changes in ALS brain organization, but disease-related changes in cortical communication remain unknown. We recruited individuals with ALS and age-matched controls to operate a brain–computer interface while electroencephalography was recorded over three sessions. Using normalized symbolic transfer entropy, we measured directed functional connectivity from frontal to parietal (feedback connectivity) and parietal to frontal (feedforward connectivity) regions. Feedback connectivity was not significantly different between groups, but feedforward connectivity was significantly higher in individuals with ALS. This result was consistent across a broad electroencephalographic spectrum (4–35 Hz), and in theta, alpha and beta frequency bands. Feedback connectivity has been associated with conscious state and was found to be independent of ALS symptom severity in this study, which may have significant implications for the detection of consciousness in individuals with advanced ALS. We suggest that increases in feedforward connectivity represent a compensatory response to the ALS-related loss of input such that sensory stimuli have sufficient strength to cross the threshold necessary for conscious processing in the global neuronal workspace.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is an adult-onset, progressive disorder that is characterized by the degeneration of upper and lower motor neurons as well as the corticospinal tract [25]. ALS has traditionally been associated almost exclusively with neurodegeneration of the motor system. More recently, growing evidence of changes in executive function, behavior, language and other higher cognitive domains suggests that ALS is a multisystem disease that also affects cortical processing [1,27]. This concept has been supported by diffusion tensor imaging (DTI) and magnetic resonance imaging (MRI) studies that have demonstrated a widespread pattern of structural alterations in the corpus callosum, frontal, temporal and parietal lobes of patients with ALS [2,3,8–10,14,16,19,31,32,40].

The functional correlates of these structural changes have been less extensively studied, and the effect of ALS on extramotor brain networks is largely unknown [38]. To date, neurophysiological studies of ALS have demonstrated patterns of functional adaptation and cortical plasticity such as abnormal recruitment and functioning of primary and nonprimary motor areas [20–22,33,39].

To gain further insight into how ALS alters exchange of information between two brain regions, we used symbolic transfer entropy to measure the directed functional brain connectivity between the frontal and parietal regions of individuals with ALS. Patterns of frontoparietal information exchange have been associated with states of consciousness [7,23,41], and the ability to process external stimuli [6,12,30]. Alterations in these patterns may reflect either an underlying source of the changes in executive function, behavior and language in individuals with ALS, or a

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http://dx.doi.org/10.1016/j.neulet.2013.03.028

compensatory mechanism to maintain such cognitive processes [1,27]. Studies examining functional cortical changes in ALS have also been limited to the resting state or the performance of a motor task, which may not be representative of the changes associated with cognitive processing. In this study, participants performed the cognitive task of operating a brain-computer interface [15], a task that also reflects the priorities of communication and the maintenance of relationships in individuals living with ALS [5] and thus may be useful in developing a clinically-relevant model of cortical changes in ALS for translational research [24]. The goal of the present study was to test the hypothesis that ALS is associated with alterations in frontoparietal communication that can be assessed with electroencephalography during a cognitive task.

2. Methods

2.1. Participants

This study was approved by the University of Michigan Medical School Institutional Review Board. Written consent was obtained from all participants who had sufficient motor ability to provide it; those who did not provided oral consent. Two groups of individuals participated in this study: the first consisted of individuals with a clinical diagnosis of ALS, recruited from the University of Michigan Motor Neuron Disease Clinic; the second consisted of individuals without ALS, who were age-matched to the ALS participants. Neither group underwent neuropsychological testing as part of this study.

2.2. Cognitive task

All participants engaged in the cognitive task of spelling a 23-character sentence using a P300-based brain-computer interface (BCI) [15]. Participants were seated approximately 1 m from a computer monitor that displayed a 6×6 grid of letters and commands. Rows and columns of the grid flashed in a seemingly random manner, while participants counted the flashes of the desired letter or command. After a specified number of flashes, the BCI selected a letter by classifying the participant's EEG patterns and presented it on the screen. Participants were asked to correct any errors that were made during the task, until the sentence was completed correctly or until the maximum time of 10 minutes had elapsed. The task was repeated over three sessions occurring on three different days, with a new sentence being presented to the participant each time.

2.3. Data acquisition and processing

EEG was collected from a 16-channel electrode cap embedded with tin electrodes (Electro-Cap International, Inc., Eaton, OH). All channels were referenced to the right mastoid and grounded to the left mastoid. Impedance for each channel was reduced below 10.0 kΩ before testing began. Signals were collected using a g.tec (Guger Technologies, Graz, Austria) 16-channel biosignal amplifier at a rate of 256 Hz, and bandpass filtered offline between 4 Hz and 35 Hz. Independent component analysis (ICA) was used to filter EOG artifact from all EEG channels. Subsequently, only electrodes from the frontal and parietal regions (F3, Fz, F4, P3, Pz, P4, PO7 and PO8) were used for analysis.

Twenty non-overlapping 10-second sequences of EEG recorded from these electrodes were randomly selected for the analysis of each session

2.4. EEG data analysis

2.4.1. Directed functional connectivity analysis

To assess alterations in cortical connectivity in individuals with ALS, we measured directed functional connectivity between the frontal and parietal regions of the brain. We quantified the degree of dependence of frontal regions on parietal regions and vice versa using normalized symbolic transfer entropy (nSTE), a nonlinear and model-free metric based on information theory [34,36]. Briefly, using nSTE, signal S_1 is said to be causally related to signal S_2 if the inclusion of S_1 results in a better prediction of the future of S_2 than signal S_2 alone.

Let $X(t)$ and $Y(t)$, $0 \le t \le T$ represent the average EEG signal over the source and target regions of the brain, where T is the duration of the signal. At time t_0, let X^P and Y^P represent the EEG signal when $0 \le t \le t_0$ - in other words, the signal past–and let X^F and Y^F represent the EEG signal when $t_0 0 \le t \le T$ - in other words, the signal future. Transfer entropy from X to Y($TE_{X\to Y}$), defined in Eq. (1), is the amount of mutual information between X^P and Y^F when Y^P is known:

$$TE_{X\to Y} = 1(Y^F; X^P|Y^P) = H(Y^F|Y^P) - H(Y^F|X^P, Y^P) \quad (1)$$

where $H(X)$ is the entropy of signal X. In other words, $TE_{X\to Y}$ represents the amount of information added by the past of source signal X when modeling the information between the past and future of target signal Y.

Symbolic transfer entropy (STE) is a more robust variation of transfer entropy, which avoids the need to subjectively select bin size in the probability calculation of mutual information [36,37]. In STE, each element in vectors X^P, Y^P, X^F and Y^F is replaced by the integer value of its relative rank in the vector. For example, $Y(t)$ is transformed to $Y'(t)$ by replacing each element with its rank in ascending order $y_j \in [1, 2, \ldots, T]$ for $j = 1, 2, \ldots T$. $Y'(t)$ is then used in Eq. (2) to calculate $\mathrm{STE}_{X\to Y}$.

Bias removal was accomplished by removing from $\mathrm{STE}_{X\to Y}$ an estimate of the STE if no causal relationship existed between source and target signals [18]. Practically, this was accomplished by reversing the first and second half of X^P, resulting in X^P_{Shuff} which retained the same signal characteristics as X^P but was completely disconnected from X^F and Y^F. STE with the shuffled source signal was calculated as in Eq. (2):

$$\mathrm{STE}^{\mathrm{Shuff}}_{X\to Y} = H(Y^F|Y^P) - H(Y^F|X^P_{\mathrm{Shuff}}, Y^P) \quad (2)$$

Subtracting $\mathrm{STE}^{\mathrm{Shuff}}_{X\to Y}$ from $\mathrm{STE}_{X\to Y}$ resulted in an unbiased estimate of STE. Finally, we normalize the unbiased STE by dividing it by the entropy within the target signal, resulting in $n\mathrm{STE}_{X\to Y}$.

$$s\mathrm{STE}_{X\to Y} = \frac{\mathrm{STE}_{X\to Y} - \mathrm{STE}^{\mathrm{Shuff}}_{X\to Y}}{H(Y^F|Y^P)} \in [0, 1] \quad (3)$$

Intuitively, $n\mathrm{STE}_{X\to Y}$ represents the fraction of information in Y^F not explained by its own past (Y^P) and explained by the past of the source signal X^P.

If X represents a parietal EEG signal and Y represents a frontal EEG signal, we can calculate three values: (1) $n\mathrm{STE}_{X\to Y}$, herein referred to as *feedforward* connectivity; (2) $n\mathrm{STE}_{Y\to X}$ herein referred to as *feedback* connectivity; and (3) *asymmetry*, A, as defined in Eq. (4):

$$A = \frac{n\mathrm{STE}_{Y\to X} - n\mathrm{STE}_{X\to Y}}{n\mathrm{STE}_{Y\to X} + n\mathrm{STE}_{X\to Y}} \quad (4)$$

If A is positive, feedback connectivity is dominant; if it is negative, feedforward connectivity is dominant. We evaluated average frontoparietal feedback and feedforward connectivity by calculating $\overline{n\mathrm{STE}}_{X\to Y}$ and $\overline{n\mathrm{STE}}_{Y\to X}$ for each participant: $\overline{n\mathrm{STE}}_{Y\to X} = \frac{1}{n_f \cdot n_p} \sum_{(i,j)=1}^{n_f, n_p} \overline{n\mathrm{STE}}_{i\to j}$, where $n_f = 3$ and $n_p = 5$.

For each participant, EEG collected from each of the three sessions was subdivided into four EEG datasets according to frequency: (1) total (4 Hz–35 Hz); (2) θ (4 Hz–8 Hz); (3) α (8 Hz–13 Hz); 4) β (13 Hz–30 Hz), yielding a total of 12 datasets per participant. δ frequencies were not included to minimize eye-blink