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Directional Brain Functional Interaction Analysis in Patients with Amyotrophic Lateral Sclerosis*

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Abstract— **Recent work has shown that a P300-based brain-computer interface (BCI) can provide effective long-term communication for individuals with amyotrophic lateral sclerosis (ALS). BCI users can experience significant variation in day-to-day BCI performance that can both frustrate and discourage users and caregivers alike. This study seeks to characterize this performance variation using measures of causality between electrode locations in scalp-EEG recorded from individuals with and without ALS during use of a P300-based BCI. Results show that there are statistically significant causal relationships between channels, particularly in the high beta frequency range, that are consistent across subject groups. Moreover, the connectivity patterns in the group with ALS appear to be more diffuse when compared to controls. These preliminary findings suggest that there may be differences in brain activity between individuals with and without ALS, as well as in the activity across successful and unsuccessful task sessions using a P300-based BCI. Ultimately, this information may lead more reliable BCI use for people with ALS.**

I. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that causes muscle weakness and atrophy as a result of degradation of the motor cortex, spinal cord, and brainstem [1]. ALS can lead to locked-in syndrome (LIS), a condition that can render the person unable to communicate. Exploring the functional brain networks in individuals with ALS can provide a better understanding of the neuropathology and possibly lead to more effective interventions [2]. Most recent studies with ALS patients have investigated the functional connectivity between different brain regions during specific cognitive tasks and resting state [3-5]. However, few existing studies characterize the effect of ALS on brain network connectivity [3, 6].

A study by Mohammadi et al. using ICA based fMRI analysis in a resting mode found a decreased connectivity in the default-mode network as well as the sensorimotor network for ALS subjects compared to healthy controls [5]. A later study by Douaud et al. using resting state fMRI data from ALS subjects found a distinct pattern of connectivity spanning sensorimotor, premotor, prefrontal and thalamic regions in the people with ALS compared to healthy controls [4]. Another recent study by Blain-Moraes et al. using normalized symbolic transfer entropy during a cognitive spelling task found a significantly higher connectivity in the parietal to frontal feed-forward connections in people with ALS compared to healthy controls. However, this study did not show a significant difference between feedback connectivity between these two groups [3].

The aim of this study is to further investigate brain connectivity in ALS by evaluating the causal relationship of scalp-EEG recording during the execution of the P300 Speller Task by people with ALS as compared to healthy controls. This analysis can provide insight to the neurophysiological differences that impact task performance and may lead to improved processing techniques for future BCIs.

II. Methodology

A. Subjects and Data Collection

Data were collected from 9 male BCI home users with a diagnosis of ALS and a functional rating scale (ALSFRS-R) scores that range from 0-32 (48 pt. scale). All of the data in the ALS group were collected in the patients' homes over 2 to 10 months [13]. Subjects with ALS exhibited considerable day-to-day variation in P300 performance. For comparison, data were collected from 13 able-bodied subjects using the same P300 paradigm in the laboratory during a single session. All studies were approved by the Institutional Review Boards of Helen Hayes Hospital or Old Dominion University.

EEG data were recorded using an elastic cap (Electro-Cap International) as shown in Figure 1. The signals were amplified using g.USBAmp amplifier (g-tec Medical Technologies) with a reference and ground to the right and left mastoid respectively, digitized at 256 Hz, and band pass filtered at 0.5-30 Hz. All data acquisition, real-time signal processing, and feedback process were controlled by BCI2000 [14]. In each run, subjects were presented by a matrix of alphanumerical letters that were flashed based on the checkerboard paradigm (CBP) [15]. Subjects were asked to attend to a predetermined sequence of target characters and silently count the number of times the target character intensified. The number of trials before feedback was given was optimized for each subject individually.

B. Adaptive Directed Transfer Function

Directed transfer function (DTF) analysis is a method which measures the causal relationship between two or more signals and can be considered the extension of the bivariate connectivity measuring methods. Adaptive directed transfer

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function (ADTF) is the extended version of DTF that has the advantage of measuring the rapid changes of the connectivity relationships between different brain regions. Specifically, it can be used for non-stationary signals and the signals with short duration such as event related potentials (ERPs) [7-9]. The method takes into account how a specific signal (i.e., brain activity) is influenced by other signals in the region of interest based on adaptive multivariate autoregressive (AMVAR) modeling.

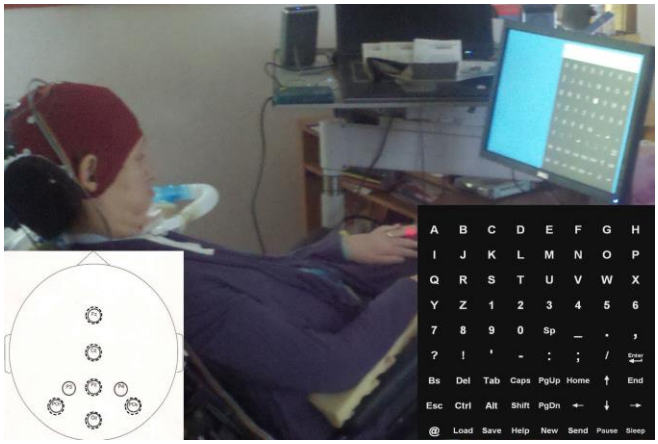

Figure 1. A subject wearing an electrode cap attends to the 9X8 matrix of items displayed on a monitor as used for calibration copy spelling in the home. Lower right inset: the 9X8 matrix. Lower left inset: the 8-channel electrode montage with the 6 electrodes used for the analysis indicated by the dashed circles.

Equation (1) shows an AMVAR model where $y(k)$ is a d-dimentional vector at time point k, $y_d$is the d^{th} dimension of y, ε is a Gaussian white noise, $A_{(r,k)}$ (i,j) is the $d\ x\ d$ dimension time varying model parameters or AMVAR model coefficients and can measure the influences from variable i to j after r time points at time point k.

$$\begin{bmatrix} y1(k) \\ y2(k) \\ . \\ . \\ . \\ yd(k) \end{bmatrix} = \sum_{r=1}^{p} A_{(r,k)} \begin{bmatrix} y1(k-r) \\ y2(k-r) \\ . \\ . \\ . \\ yd(k-r) \end{bmatrix} + \begin{bmatrix} \varepsilon 1(k) \\ \varepsilon 2(k) \\ . \\ . \\ . \\ \varepsilon d(k) \end{bmatrix} \quad (1)$$

p is the AMVAR model order which can be optimally determined based on Final Prediction Error (FPE) criterion [10] and Schwarz Bayesian Criterion (SBC) [11]. The coefficient matrix A can be estimated based on Kalman filter algorithm [12]. By getting the Fourier transform of the estimated time varying AMVAR coefficients A we can obtain $A_k(f)$ which shows the AMVAR coefficients at both time point k and frequency f as below:

$$A_k(f) = \sum_{r=1}^{p} A_{(r,k)} e^{-i2\pi fr} \quad (2)$$

We can write the transfer function of the multivariate regression model in equation (1) as below:

$$H_k(f) = [I - A_k(f)]^{-1} \quad (3)$$

Using the time varying transfer matrix elements obtained from equation (3), the ADTF values can be determined as below [8]:

$$\gamma_{ij}^2(f,k) = \frac{|H_{(k,i,j)}(f)|^2}{\sum_{m=1}^{H} |H_{(k,i,m)}(f)|^2} \quad (4)$$

where H is the number of channels.

C. Connectivity Statistical Analysis

The resulting ADTF values cannot be evaluated until a significance test is performed to compare the resulting connectivity values to the values obtained from surrogate data. The method for generating the surrogate data used for the present analysis was based on phase shuffling, which preserves the power spectrum of the signal as well as the linear correlation between the time series. To do this, the FFT of the original signal was obtained and the resulting phase angles were shuffled using a random permutation of the order. An inverse FFT was used to convert the phase-shuffled signal back to the time domain. This shuffling process is repeated many times and the significant connectivity is computed based on the distributions generated by the surrogate data.

D. Data Processing

Due to the considerable day-to-day performance variations for the ALS subjects, runs with actual online accuracies $\geq$ 70% were labeled as successful and all other runs were labelled as unsuccessful [16]. All runs for the control group were successful using this criterion.

Six EEG channels that are standard for the P300 speller were used to assess brain connectivity: Fz, Cz, Pz, PO7, PO8, and Oz [13]. Average target ERPs segmented from 0-800 ms were used for the connectivity analysis. For consistency, the first 360 trials related to the target ERPs for both successful and unsuccessful runs of both groups were included in the analysis. For each trial, baseline correction was performed by removing the mean of each response. Significant ADTF values were obtained using eConnectome software [8] with the maximum model order set to 5. The statistical test was performed using 200 surrogate samples with a significance level of $\alpha = 0.05$.

The significant and the non-significant ADTF values were set to 1 and 0, respectively, to show the percentage of subjects with significant connectivity values for each connection and time point. To investigate the connectivity pattern in different frequency bands, the values averaged over the frequency bands of interest; delta (1-3 Hz), theta (4-7 Hz), alpha (8-14 Hz), low beta (15-18 Hz) and high beta (19-30 Hz).

III. Results

For the healthy controls there was little significant connectivity outside of the high-beta band. For the ALS group, significant connectivity was found in the high-beta band, and broadly distributed in the other frequency bands as compared to the controls. Thus, the analysis is focused on the high-beta band for both subject groups. Figure 2 shows the percentage of subjects in each group with significant high-beta band ADTF values for all the channel pairs and time points. For the ALS subjects, the connectivity analysis was computed on the successful and unsuccessful runs separately.

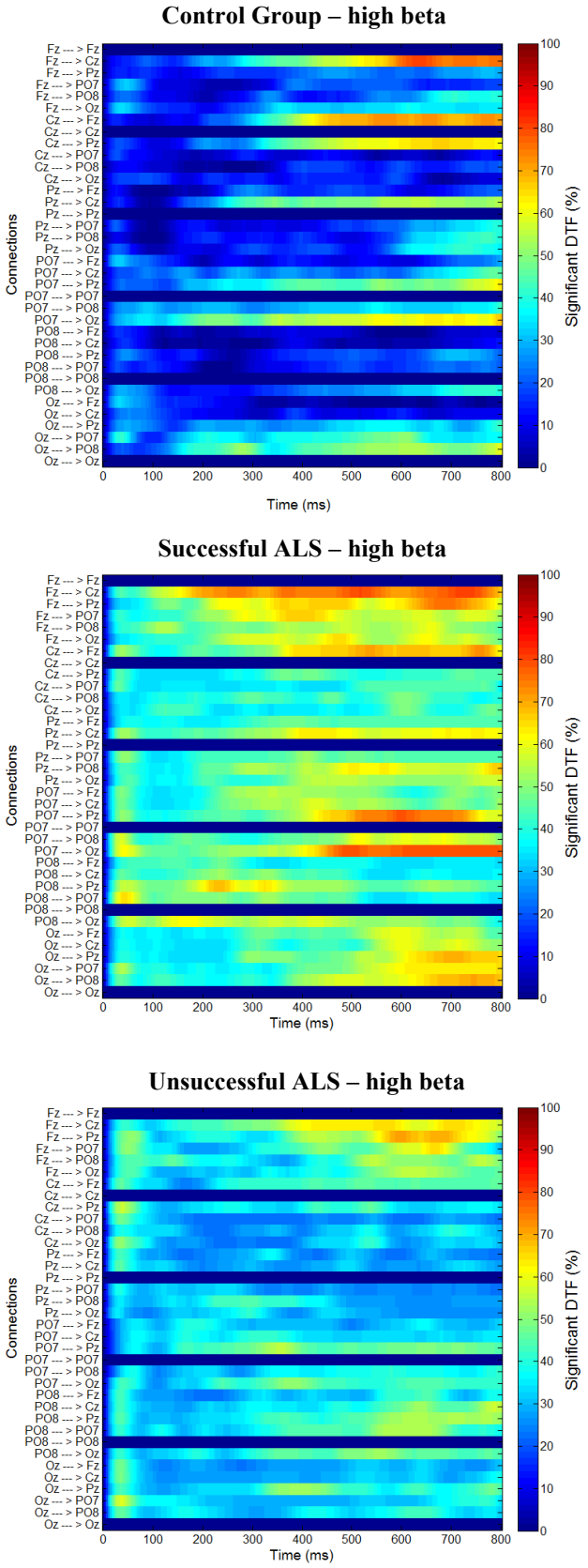

Figure 2. The percentage of significant high-beta band ADTF values for all subjects. Top: controls (all successful), Middle: successful ALS runs, Bottom: unsuccessful ALS runs.

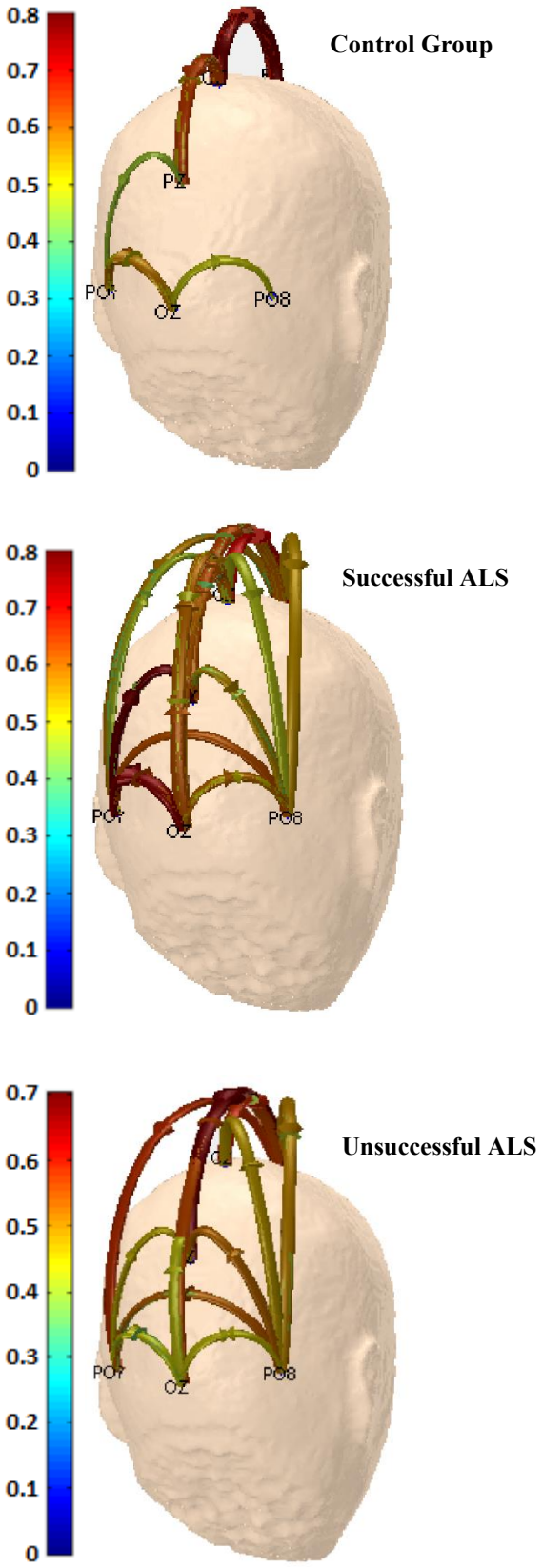

Figure 3. The percentage of signal outflow to inflow information rate for the high-beta band at t = 600 ms. Top: controls (all successful), Middle: successful ALS runs, Bottom: unsuccessful ALS runs

Figure 3 shows the percentage of signal outflow to inflow information rate for the high-beta band at t = 600 ms. This time point represents the location of the highest percentage of subjects with significant ADTF values across subject groups. This directional arrows illustrate the information flow of connectivity between two channels. The color and width of arrows correspond to the percentage of subjects having a statistically significant information flow rate. Only connections in the range of 50% to 100% of the maximum value are displayed.

IV. Discussion

There was higher percentage of subjects with significant connectivity in both subject groups in the high-beta band compared with the other frequency bands. These findings can possibly be explained by the association of networks of inhibitory inter-neurons with the neural oscillations in the beta frequency range [17]. The results also indicate a generally broader distribution of significant connections for the ALS patients compared with the control group. This corresponds with the findings obtained by Douaud et al. [4], which attributed the increased brain connectivity in ALS patients to a physiological, compensatory response to disease-related loss of structural network integrity. However, this broader distribution may also be partially attributed to higher variability in the connectivity patterns for the ALS group.

It is interesting to note that the channel pairs and approximate time instances with the highest percentage of significant beta-band connectivity across subjects are consistent for the successful ALS runs and the control group, which consists of all successful runs. This may be associated with task engagement for the successful runs since this pattern appears sufficiently suppressed for unsuccessful ALS runs. It is also interesting to note that the highest percentage of peak activity is observed around 600 ms at the bidirectional connection of Fz-Cz for the ALS and control groups. While the peak of the P300 is generally later for ALS patients, this connectivity analysis may reflect common connectivity patterns in the later stages of the P300 response across groups. The directivity analysis shows that there are few, very distinct connections that only exist between adjacent electrode pairs for the control group. The information flow at 600 ms is largely focused bi-directionally at Cz, with PO7 flowing to Pz and Oz. The highest percentage of flow is from Fz to Cz. In contrast, there are complex information flow patterns for both the successful and unsuccessful runs of the ALS patients. This also supports the findings in Douaud et al. [4], but does not clearly discriminate the performance groupings.

The purpose of this study was to determine if a comparison of measures of causality derived from EEG data recorded from people with and without ALS while using a P300-based BCI could shed light on day-to-day variations observed during home use by people with ALS. These preliminary findings suggest that there may be differences in brain activity between individuals with and without ALS, and, more importantly, between successful and unsuccessful sessions. As expected, the number of significant connections was lower for the unsuccessful ALS group as compared to the successful ALS group and the control group. Consistent with prior research, both of the ALS groups exhibited more overall connectivity than the control group, although it remains unclear whether this is a result of inter-subject variability or more expansive connectivity in ALS subjects. Based on these results, criteria can be established to provide home users with information about their readiness to use a BCI. Ultimately, it may lead to improved methods to assess and improve BCI performance for all BCI users.

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