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CASE STUDY: TRADITIONAL MOTOR CORTEX CONTROL FEATURES IN ALS AND BRAINSTEM STROKE

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ABSTRACT: The goal of the Utrecht NeuroProsthesis (UNP) study conducted at the UMC Utrecht is to evaluate the usability of a BCI system for communication in people suffering from Locked-In Syndrome (LIS): people who cannot speak due to a loss of almost all motor control. In the past we demonstrated that a combination of High Frequency Band (HFB) and Low Frequency Band Sensorimotor cortex (SMC) features can be used to provide an individual with LIS due to ALS with a stable and robust communication channel. The recent inclusion of a second LIS participant in the UNP study, a woman who suffered a brainstem stroke, enables us to compare SMC LFB and HFB features in people with LIS caused by two fundamentally different etiologies. We show that while the HFB is a stable feature in both cases, the functional stability of the LFB feature is much less in the brain stem stroke subject.

INTRODUCTION

It is the goal of the BCI research group at the UMC Utrecht to develop and validate devices that will provide people suffering from Locked-In Syndrome (LIS) with a reliable means of communication that works 24/7. People with LIS are quadriplegic, anarthric and are generally only able to move their eyes, but they are conscious of thought [1]. Having a reliable channel for communication has the potential to improve the quality of life and the integration into society of these individuals [2,3].

In a recent report, we demonstrated that a combination of High Frequency Band (HFB) (31-100Hz) and Low Frequency Band (6-30Hz) signal changes, as measured from the motor cortex using subdural electrocorticography (ECoG), can be used to create a robust and stable BCI communication channel in an individual with LIS due to late-stage ALS [4]. The amplitude changes produced in these frequency bands by the participant attempting to move her hand were in close agreement with those traditionally associated with sensorimotor cortex (SMC) function and the generation of movement [5,6]. However, the LIS condition may be caused by multiple clinical conditions, including ALS and brain stem stroke. Whereas multiple studies using EEG [7-8], ECoG [4, 9-10], and intracortical electrodes [11-12] have now proven the feasibility of SMC BCI control in individuals with severe paralysis, little is known about the relation between etiology and SMC neuroelectrical signal characteristics and BCI control ability. The inclusion and implantation of a second participant in the UNP study of an individual who suffers from LIS due a to a brainstem stroke provides a unique opportunity to compare the LFB and HFB features in individuals with different causes of LIS [2,13]. The current study analyses cortical electrical potentials collected regularly over an extended (> 60 week) period from ECoG electrodes implanted over the SMC while participants performed a standardized attempted movement task. Both the functional stability of the LFB and HFB features and the spectral characteristics of the LFB feature are compared and put into the context of the UNP users' specific clinical conditions. We believe that this work can inform the development of future SMC-BCI systems that target people with LIS.

MATERALS AND METHODS

UNP Participants: The medical research ethics committee of the UMC Utrecht approved the UNP study, which was carried out in accordance with the Declaration of Helsinki (2013). Participants gave informed consent through a dedicated procedure (described in detail in [4]: supplementary materials). All work presented here is part of this continuing study. The first participant (UNP1), data of whom were reported in [4], is a woman who was diagnosed with ALS in 2008. She was 58 years old at the time of informed consent in 2015. She was put on invasive ventilation in 2010 and was living with minimal motor control for around 5 years at the time of implantation of the UNP in October of 2015. She had a score of 2/48 on the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) [14]. For communication she used, and continues to use, an eye tracker to type and eye blinks, and (lately) small movements of the mouth corner, to answer closed questions. In addition, she now uses the UNP system for communication on a routine basis.

The second UNP participant (UNP4) is a woman who suffered a brain stem stroke in 2004 and who was 39 years old at the time of informed consent in August of 2017. Her motor capabilities are limited to neck

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movements and facial expressions and she had been living with LIS for 13 years at the time of inclusion in the UNP study. She uses a head switch to control scanning software for typing, and horizontal and vertical eye and head movements for answering closed questions. She has a score of 17/48 on the ALSFRS.

UNP ECoG signal: The primary cognitive strategy used to control the UNP device for both subjects is attempted movements of the contralateral (right) hand. Corresponding ECoG signal changes are recorded using subdural electrodes implanted over the 'hand knob' of the sensorimotor cortex (see Figure 1 of [4] for a depiction of the electrode locations in UNP1).
The implant target location was determined prior to surgery using fMRI scans. Subdural electrode strips (Resume II®, Medtronic, 4 electrodes each, 4mm diameter, 1cm distance, off label use) were implanted through burr holes (1cm diameter), over the target areas. An amplifier/transmitter device (Activa® PC+S, Medtronic, off label use) was placed subcutaneously under the clavicle. In addition to the online control mode of this device, in which analog filtered spectral amplitude signal is relayed to a receiving tablet at 5Hz (see [4] Methods for details), the device offers transmission of non-filtered 'raw' time domain signals at 200Hz. This work uses off-line analysis of the time domain signal recorded during repeated attempted hand movements to create time-locked responses in the frequency domain.

Attempted hand movement screening task: In order to track the functional response of the signal features subjects periodically performed a screening task that involved making repetitive attempted hand movements, or relax, for alternating periods of 15s each. In total 50 runs consisting of either 10 (17 runs) or 4 (33 runs) alternated rest and attempted movement trials were performed by UNP1. UNP4 completed 46 runs of the task, each with 6 trials of repeated attempted hand movements and relaxation.

Spectral analysis: The amplitude for each frequency bin from 6 to 100Hz (in steps of 1Hz) was computed offline for every time sample of each time domain data file using the real component of the convolution with a complex gabor wavelet (span 4 cycles at fwhm) [15]. The LFB and HFB responses over time were then computed as the sum of the log of the amplitudes for the frequency ranges 6-30Hz and 31-100Hz, respectively. These ranges were chosen based on the match to LFB and HFB ranges reported in literature [5,6].

Evaluation of- functional response features: Prior analysis of data acquired from UNP1 during the screening task [16] indicated that attempted hand moments produce 3 distinct functional response periods in the signal that are well matched to those reported in ECoG literature [5,6,17]. The 3 periods are: 1) the active period of the task during which the participant attempts to move the hand, 2) a 3 second rebound period directly following the cue to stop making attempted movements. and 3) the rest period, directly following the rebound period, during with participants relax and wait for next cue. Based on this knowledge, the following 3 expected functional responses were quantified: 1) The increase in mean HFB amplitude for active trials vs. rest periods, 2) the decrease in mean LFB amplitude during active trials vs. rest periods, and 3) the increase in LFB mean amplitude during the rebound periods following active trials, vs. rest periods. In the current study, these three functional responses were quantified for each task run using the coefficient of determination (R-squared) statistic over the mean amplitudes of each trail. A significance cut-off of $p < 0.05$ was used to determine significance.
The percentage of task runs with significant responses was also computed and used to compare the two UNP subjects. However, the fact that only two subjects are reported prevents statistical testing of the differences between to subjects.

Oscillatory signal component analysis: To gain a better understanding of the underlying spectral changes leading to the LFB and HFB functional responses both the spectral content of the active trials and rest periods of the screening task and that of separate baseline data sets, during which the UNP subjects simply relaxed and not concentrated on a task, was analyzed.
First, the spectral amplitude over time (see section *Spectral analysis*) was computed for 52 and 32 baseline data sets of 2-5 minutes each- for UNP1 and UNP4 respectively. Then the mean amplitude profile (from 4 to 40Hz) was computed along with the profile of the standard deviation. Here we used a slightly broader LFB range in order to evaluate if the trends in LFB spectral response may have been affected by neighboring frequencies beyond the traditional LFB boundaries.
Next irregular-resampling auto-spectral analysis (IRASA) [18] was used to separate the oscillatory spectral peaks from the scale-free (or fractal) component of the spectra during rest and active periods of the attempted movement task. This procedure allows for a direct comparison of the LFB oscillatory profiles that corrects for differences in spectra profiles due to differences in electrode impedances over runs or signal amplifiers between subjects. Again, a range of 4-40Hz was used. A 3s moving window with step size of 1s was used to divide the data into many time samples of rest and active periods. Windows that crossed the boundary between active and rest periods or that included data from rebound periods were excluded.

RESULTS

As reported earlier [4] the functional stability of the HFB and LFB responses of UNP1 was remarkably high. In fact, 100% of the runs produced HFB responses that were significant at the 0.05 p-value level and 98% of the runs had a significant LFB response. In addition to these, the LFB rebound response (green points) also presents a stable signal feature over the same period (with 90% of the runs having a p-value < 0.05).

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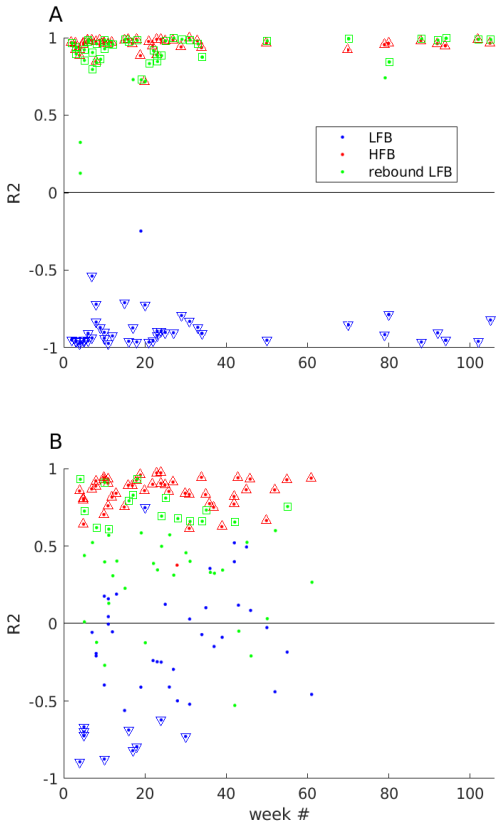

Figure 1: Functional consistency of the HFB and LFB responses of UNP1 and UNP4 over 106 and 61 weeks after implantation. A) The R-squared values of the HFB response (red dots), LFB response (blue dots) and LFB rebound response (green dots) over all task runs for UNP1. Runs with significant responses (p-values <0.05) are indicated with the red upward pointing triangle, blue downward pointing triangle, and green squares for the three response respectively. B) The R-squared values of the HFB response, LFB response, and LFB rebound response over all task runs for UNP4.

In contrast to UNP1, and despite the fact that UNP4's HFB functional response is only slightly less consistent (97.8% of runs showing a significant HFB response) than that of UNP1, the LFB responses generated by UNP4 during the screening task were considerably less functionally stable (21.7% of the runs have a significant LFB response; see Figure 1B). In addition, also the LFB rebound functional feature is much less consistent over runs (34.8% runs show a significant LFB rebound). Importantly, there was no clear trend in improvement in these features over time (Figure 1B).

The lack of significant LFB responses in UNP4 could be due to one or both of two phenomena: 1) a weak or changing oscillatory component during rest leads to low average LFB amplitudes during the rest condition, or 2) poor functional regulation of the LFB oscillatory component which then leads to mean amplitudes of the LFB remaining relatively high during active periods of the task. To gain further insight into the LFB signal we analyzed the spectral content of the LFB feature during the baseline and screening tasks.

When looking at UNP1's LFB signal during the baseline task (Figure 2A left) the mean spectra show a broad peak between 12 and 26 Hz, with the lowest variance within and between runs around 25Hz. This same peak can be seen in the mixed spectra during rest periods of the screening task (blue line Figure 2B left). Indeed, isolated oscillatory components are present in the 10Hz to 27Hz range of the rest periods (Figure 2C left), with the most consistency over runs between 22Hz and 26Hz. This oscillatory component is not present during the active periods of the task. In addition, there is a smaller distinct oscillatory peak around 8Hz that remains present during active periods. Overall these results fit with a model of LFB activity during rest that is diminished with motor cortex activation.

UNP4 demonstrates a spectral bump from 6Hz to around 22Hz in baseline runs (Figure 2A right). However, the peak of oscillatory activity during rest periods of the task is focused between 7Hz and 10Hz and remains present, although to a lesser degree, during active periods (Figure 2B/C right). Thus, while there is evidence of a LFB oscillatory peak in the motor cortex of UNP4, this peak is constrained to the Mu band (6-12Hz), with the least variance at 7-8Hz, and hardly changes during active periods. Both the fact that there is a less distinct peak in the LFB during rest and the fact that this peak remains present to a certain degree during active periods could contribute to the decreased functional difference in the LFB during attempted hand movements for UNP4.

DISCUSSION

In is study we evaluated three distinct functional features of the SMC neuroelectrical ECoG signal in the context of two BCI users in the LIS state with different underlying etiology. Participant UNP1 suffered from ALS which is a neural degenerative disease that affects both upper and lower motor neurons [19]. UNP4 suffered from a brain stem stroke, which caused extensive damage to the brainstem. While both UNP1 and UNP4 have a functionally consistent HFB feature (present in >97% of attempted movement task runs) the work presented here shows a considerable discrepancy in both the functional consistency and oscillatory content of the LFB features between the participants. Here we discuss this result in the context of 1) the traditional SMC LFB functional feature reported in literature and 2) the reported effects of ALS and stroke on these frequency features.

Traditional ECoG SMC functional signal features: The HFB feature has been shown to be ubiquitous to human neocortex [20] and is associated with focal increases in asynchronous neural activity in response to executed, imagined or attempted movement [13-23].

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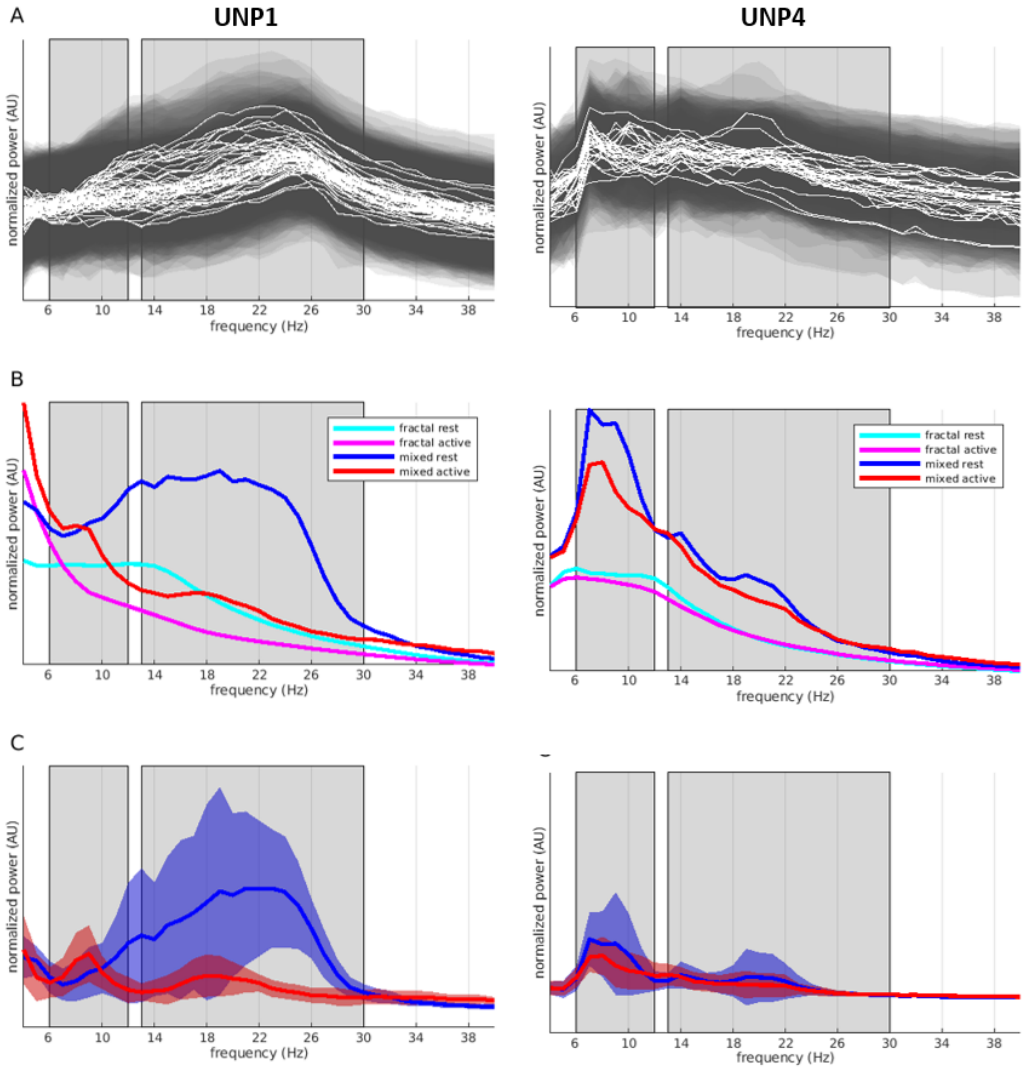

Figure 2: Oscillatory content of the LFB for UNP1 (left column) and UNP4 (right column). A) LFB spectra during baseline task. The mean (white lines) spectrum from 4-40Hz is plot for each run. The semi-transparent grey shaded regions indicate the plus and minus 1 standard deviation boundaries for each run. B) The mean (over runs) fractal spectral profiles for the rest (cyan line) and active (magenta line) periods and the mixed (fractal+oscillatory) spectral profiles for the rest (blue line) and active (red line) periods. C) The mean oscillatory profiles over runs of the rest (blue line) and active (red line) periods. The blue and red shaded regions indicate the rest and active plus and minus 1 standard deviation boundaries respectively.

In the case of the UNP1 it was previously demonstrated that reliable click-based spelling control was dependent on a combination of the HFB feature and an LFB feature [4], the spectral range of which (~6-35Hz) is consistent with that of the classic LFB spectral feature of motor cortex reported in ECoG literature [6,23]. This LFB feature overlaps with the Mu-band (6-12 Hz) motor rhythm often used in EEG-based motor BCI [24], and with other oscillatory features commonly reported in EEG and ECoG literature such as the Theta (4-7Hz) [25], and Beta (12-30Hz) [26] bands. The common term for the observed decrease in amplitude of these bands associated with cortical activation is Event Related Desynchronization (ERD). While the neuronal mechanisms underlying ERD are still being studied and may differ for different LFB sub-bands, the functional significance generally attributed to ERD is the release of inhibitory input on the measured neural population to allow cortical processing, which is reflected in the increase in HFB amplitudes.

The results of UNP1 fit with a model of Beta band desynchronization during motor cortex activation by attempted hand movement. However, there seems to be a lack of ERD in the mu-band. This suggests that Beta and Mu may have different generative sources that are differentially affected by ALS.

UNP4 shows little evidence of baseline Beta band activity suggesting disruption of the generative source for Beta band synchronization. The lack of functional consistency in the LFB rebound is in agreement with a disruption in the Beta band signal generation. Indeed, the Beta band has been most closely linked to Event Related Synchronization (ERS) after movement offset [27-28]. In

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addition, attempted movement of the hand hardly affects LFB power, suggesting weak functional regulation. Although the LFB feature of UNP4 does show evidence of Mu activity, both the functional consistency analysis and oscillatory analysis results indicate that there is a disruption in the ERD of the Mu band as well.

Effects of ALS and Stroke on the LFB functional feature: Since ALS and brainstem stroke are fundamentally different neural motor afflictions it can be expected that the effect of these conditions on the functional features of SMC ECoG signal will differ. Here we discuss our findings in the context of the relatively small body of work addressing LFB (functional) features in stroke and ALS.

One study with 13 individuals who suffered a brainstem stroke reported higher levels of resting state alpha band (comparable to Mu) throughout the cortex, including the central areas [29]. This is interesting in light of our finding that there is a Mu oscillatory peak in UNP1 and UNP4 that persists during active periods. Both decreased Beta band motor ERD [30-31] and decreased Mu band ERD [32] have been reported in chronic stroke subjects. However, these studies focused on cortical and subcortical stroke and did not include any brain stem stoke subjects. While the lack of a Beta peak within the LFB feature, and persistence in Mu band oscillatory activity during active periods are both in agreement with this literature, the considerable differences in affected areas of cortical and brainstem stroke make it likely that other factors underlie the findings presented here than those in cortical stroke patents.

Several studies have addressed the resting state levels of LFB amplitudes in LIS ALS subjects. An EEG study with 8 LIS ALS subjects [33] and an ECoG study with one LIS ALS subject [34] both reported relatively more Theta power and less HFB power in baseline activity. While we did not specifically test for this effect in the baseline signal, a decrease in baseline HFB power could contribute to the robustness of the functional increase of HFB amplitude over rest period levels in our ALS subject. In studies of ALS subjects a decreased ERD [35-36] has been reported and correlated to disease progression [35]. However, another study reports an increase in ERD [37] while two more report no change [38-39]. Thus, the reported effects of ALS on ERD are inconsistent. In contrast, when reported, ERS has been reported to decrease in effect size [38]. However, this study included no ALS subjects who had reached the LIS stage. Our finding that ERS is very robust in the ALS LIS subject may be associated with the far progressed stage of the disease, but this topic deserves further investigation.

CONCLUSION

Our results indicate that while the HFB remains a stable SMC functional feature in two individuals with LIS with fundamentally different etiologies the functional stability of the LFB feature is much less in the brain stem stroke subject. Although these findings need to be confirmed in a larger population, they highlight the need to consider individual etiologies when designing SMC based BCIs targeted at individuals with LIS.

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