Sensorimotor rhythm modulation depends on resting-state oscillations and cortex integrity in severely paralyzed stroke patients

Eduardo López-Larraz[1,*], Andreas M. Ray[1], Niels Birbaumer[1,2], Ander Ramos-Murguialday[1,3]

***Abstract*— Alpha oscillatory activity and its dynamics have a key role in motor and sensory functions. Stroke affects different brain structures, which can result in pathological changes in alpha oscillations. We studied the relationship between the amplitude of alpha oscillations in resting state and their modulation during the attempt of movement in 37 patients with severe paralysis after stroke. As previously observed in healthy subjects, resting-state alpha activity significantly correlated with the alpha event-related desynchronization (ERD) during the attempt of movement of the paralyzed hand. Further, alpha ERD correlated with the presence or absence of damage in cortical structures, but resting-state alpha power did not. This result provides new insights on the understanding of the brain changes after stroke, which may help in future therapies to help the patients to recover their lost motor function.**

I. Introduction

Oscillatory alpha activity is the dominant rhythm in the human electroencephalogram (EEG). Its fundamental role in abilities like memory, attention and information processing has been deeply studied during the last decades [1], [2]. Alpha oscillations recorded in the sensorimotor cortex (also referred to as the sensorimotor or mu rhythm) are a major topic of research due to their relationship with motor and sensory processing [3]. For instance, they have been related to inhibitory control [4] and tactile perception [5].

The way the brain activates during motor and sensory tasks is reflected in the EEG as a power reduction of sensorimotor alpha activity. This phenomenon, termed as the event-related desynchronization (ERD), indicates a decrease in synchrony of neural firing [3]; in contrast to the event-related synchronization (ERS), which reflects an increase in synchrony related to cortical idling [3]. Accordingly, stronger ERD (i.e., greater power reduction of ongoing oscillations) implies stronger brain activation [6]. These ERD/ERS phenomena are computed relative to a segment of activity recorded in resting state, to quantify the change in brain activity during a certain task with respect to inactivity. Interestingly, the amplitude (or power) of the alpha oscillations during rest influences the subsequent alpha ERD during movement [7], [8], which suggests that the basal state of the brain denotes its potential to activate to a greater or lesser extent [9].

After a stroke, several brain networks are damaged, leading to a pathological brain function, and in many cases, to long-lasting paralysis. Current trends in neurorehabilitation proposed ways to reestablish the damaged brain by activating plasticity mechanisms with the ultimate goal of facilitating functional recovery [10]. The use of brain/neural-machine interfaces (BMI) to reconnect the impaired brain with the paralyzed limbs has demonstrated a great potential to promote motor recovery in these patients [11], [12]. The BMIs generally rely on classifying the alpha ERD patterns over the motor cortex during the attempts of movement of a paralyzed limb to facilitate that movement with an external device, such as a robotic exoskeleton. A better understanding of how alpha oscillations and their modulation during movement attempts (i.e., the ERD) are affected after stroke might help to redesign and improve the therapies based on BMI.

In this study, we investigate the relationship between the alpha oscillations in resting state and the modulation of their amplitude during movement attempts (i.e., the alpha ERD) in patients with severe paralysis due to stroke. We analyzed EEG data of 37 chronic stroke patients with severe upper-limb paralysis. Following previous evidence from healthy subjects [7], [8], we tested if after brain damage due to stroke, higher alpha activity during rest leads to a greater alpha ERD during the attempt of an impossible movement. Further, we investigated the role of the location of the stroke in this phenomenon. Therefore, we studied if stroke lesions affecting the motor cortex result in different changes in resting-state alpha activity or in alpha ERD compared to lesions affecting subcortical structures only.

II. Methods

A. Patients

Thirty seven chronic stroke patients (15 female, age 54.5±11.9 years, time since stroke 63.9±56.8 months) were recruited for a BMI-based rehabilitation intervention [13], although the data analyzed in this paper corresponds to a pre-intervention screening, recorded before starting the therapy. All the patients suffered complete hand paralysis with no residual finger extension in the affected arm. Sixteen patients had lesions that involved subcortical structures only and the other 21 had mixed lesions (i.e., involving cortical and subcortical areas). Table I summarizes demographic details of the patients and their impairment measured with the modified upper-limb Fugl-Meyer assessment (FMA, excluding coordination, speed and reflexes; max. 54 points). The experiments were performed at the University of Tübingen (Germany). The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Tübingen, and all the patients provided written informed consent before participation.

[1]Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Silcher Str. 5, 72076, Tübingen, Germany.
[2]Wyss Center for Bio and Neuroengineering, Geneva, Switzerland.
[3]TECNALIA Health Technologies, San Sebastian, Spain.
*Correspondence: eduardo.lopez-larraz@uni-tuebingen.de

TABLE I

SUMMARY OF THE PATIENTS

Group	Gender	Age (yr)	Time since stroke (mo)	Lesion side	FMA Score
Subcortical	9M/7F	55.6±10.3	71.1±50.6	8R/8L	12.5±10.1
Mixed	13M/8F	53.7±13.2	58.5±61.7	15R/6L	11.6±8.3

B. Experimental protocol and data acquisition

The patients participated in one screening session, where their electroencephalographic (EEG) and electromyographic (EMG) activity was recorded while they attempted to move their completely paralyzed hand. Each patient executed between 4 and 6 blocks of 17 trials each, in which they were asked to try to open and close the affected hand. Audiovisual cues were presented to the patients to indicate them when to rest (random duration between 4-5 seconds), when to attempt the movement (for 4 seconds), and the inter-trial intervals (random duration between 8-9 seconds).

EEG activity was recorded with a 16-electrodes Acticap system (BrainProducts GmbH, Germany) from Fp1, Fp2, F3, Fz, F4, T7, C3, Cz, C4, T8, CP3, CP4, P3, Pz, P4, and Oz locations, with the ground in AFz and reference in FCz. Vertical and horizontal electrooculographic (EOG) derivations were recorded to capture eye movements. EMG activity was recorded using bipolar Ag/AgCl electrodes (Myotronics-Noromed, USA) from four muscles: *extensor carpi ulnaris*, *extensor digitorum*, *biceps* and *triceps*. All signals were synchronously sampled at 500 Hz.

C. Data pre-processing

The EEG signals were band-pass filtered in the range 0.1-48 Hz (4th-order causal Butterworth filter) and trimmed down to 7-second trials (from -3 to +4 s with respect to the cue instructing the patients to start the movement).

The data of each patient were separately processed with an automatic procedure based on EEG, EOG and EMG to minimize the influence of artifacts [14]. First, ocular contaminations in the EEG were filtered using linear regression with the EOG derivations. Subsequently, trials were considered as artifacts and rejected if presented: (1) muscle activation during the rest periods in any of the EMG electrodes, or during the movement attempt periods in the EMG electrodes of the opposite arm; or (2) motion or muscular artifacts in the EEG (computed by z-scoring the power in delta and gamma frequencies and discarding trials that exceeded in more than 3 std of the power during rest). Subsequently, the EEG signals were re-referenced using small Laplacian derivations to reduce the effect of volume conduction.

D. Data analysis

The average time-frequency response for each patient was calculated with all her/his available trials (after artifact rejection) using Morlet Wavelets in the frequency range [1-30] Hz, with a resolution of 0.25 Hz. The EEG electrode placed over the hand motor area of the ipsilesional hemisphere was selected for further analyses (i.e., C3/C4 for patients with right/left-hand paralysis, respectively). We estimated the alpha power in resting-state and the alpha event-related desynchronization/synchronization (ERD/ERS) during the attempt of movement. The alpha rhythm was defined as the range of frequencies between 7 and 13 Hz.

1) Resting-state power: To calculate the alpha power during rest, we integrated the power values in the alpha range within the time interval [-2.5, -0.5] s. The resulting value was normalized by diving it by the integral over the whole power spectrum (i.e., [1-30 Hz]) in the same time interval.

2) Event-related (de)synchronization (ERD/ERS): To obtain the cortical activation during movement attempt, we employed the formula: $ERD/ERS = \frac{A-R}{R} \times 100$, where *A* is the mean alpha power during the interval [0.5, 3.5] s and *R* is the mean alpha power during the interval [-2.5, -0.5] s.

As a complementary analysis, we evaluated the relationship between resting state activity and the activity during movement attempt (ERD/ERS) in delta ([1-3] Hz), theta ([4-6] Hz) and beta ([14-30] Hz) frequency bands.

E. Statistics

Firstly, we studied the relationship between resting-state alpha power and the subsequent ERD/ERS during movement attempt by computing the Spearman's correlation coefficient (ρ). Secondly, we compared if the type of stroke (i.e., subcortical or mixed) had an influence either on the resting-state alpha power or on the ERD/ERS during movement attempt by using two-tailed Mann–Whitney U tests.

III. RESULTS

One of the patients (with subcortical lesion) was discarded due to the excessive amount of artifacts in the data. Therefore, all the subsequent results refer to the data of the remaining 36 patients.

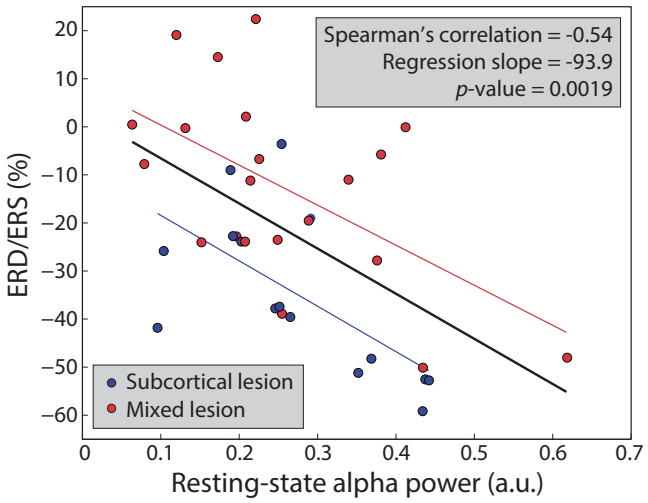

Fig. 1. Relationship between resting-state alpha power and ERD/ERS during movement attempt. Each point corresponds to one patient. The type of lesion of each patient is color-coded (blue = subcortical; red = mixed). The regression line fitted for all the patients is marked in black. The regression line fitted for the subcortical/mixed patients only is marked in blue/red.

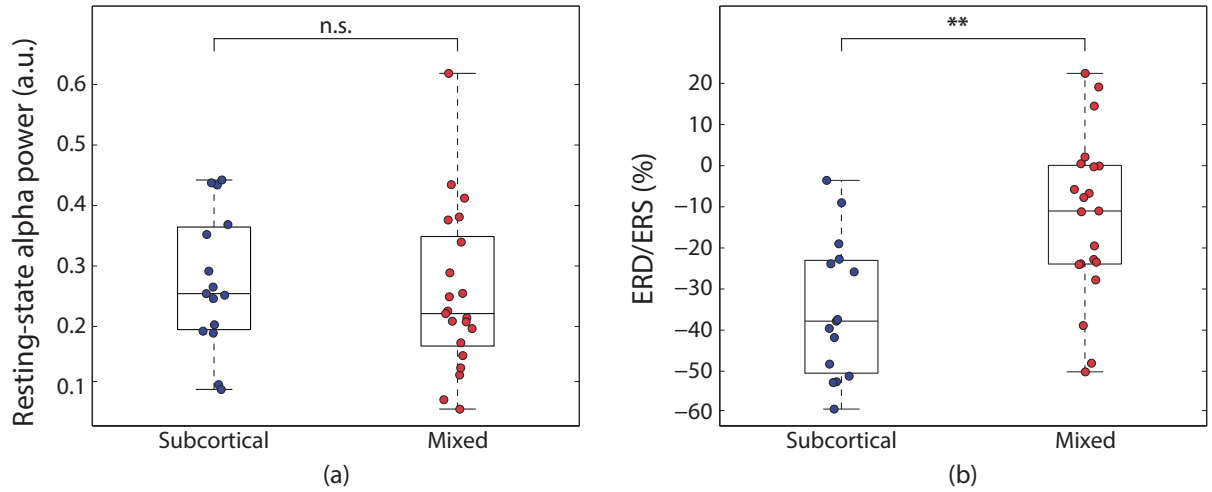

Fig. 2. Bloxpots comparing the differences between subcortical and mixed stroke in terms of resting-state alpha power (a) and ERD/ERS (b). The power values are normalized between 0 and 1 as they represent the relative alpha power ([7-13] Hz) with respect to the whole power spectrum ([1-30] Hz). Negative ERD/ERS values represent desynchronization, i.e., reduction of alpha power with respect to the resting baseline. The results of the paired statistical comparisons are also displayed. n.s. = non-significant; ** = $p < 0.01$

We found a statistically significant negative correlation between the alpha power in resting-state and the alpha ERD/ERS during the attempt of movement of the paralyzed hand ($\rho = -0.54$, $p = 0.0019$; Figure 1). This indicates that those patients with higher alpha power during rest present a larger modulation of this rhythm during movement attempts. We repeated the correlation analysis separately for both patient groups (subcortical and mixed stroke). The negative correlation was also significant both for the subcortical ($\rho = -0.63$, $p = 0.0141$, blue line in Figure 1) and for the mixed ($\rho = -0.46$, $p = 0.0351$, red line in Figure 1) groups separately.

We further analyzed the influence of the lesion location on the resting-state alpha power and on the ERD/ERS (Figure 2). We found that alpha power during rest is not affected by the location of the stroke ($U = 134$, $p = 0.45$), but ERD/ERS is significantly affected ($U = 62$, $p = 0.002$). Patients with subcortical stroke showed an ERD of higher magnitude (i.e., more negative) than patients with mixed stroke (Figure 2b).

The complementary analysis on delta, theta and beta frequencies revealed no statistically significant correlation between resting-state activity and the activity during movement attempt in these bands (Figure 3).

IV. Discussion and Conclusions

In this paper, we confirmed the significant relationship between the power of alpha oscillations in resting state and the degree of activation of the motor cortex (measured as the alpha ERD) during the attempt of movement of a paralyzed limb in patients with chronic stroke. This is a phenomenon that had already been described in healthy subjects [7], [8], but not in patients with severe paralysis due to stroke.

We also aimed at understanding if this relationship depends to some extent on the location of the stroke. We separated the patients into two groups (patients with lesions affecting subcortical structures only or affecting cortical and subcortical areas) and observed that the relationship between alpha amplitude and ERD was similar in both groups. However, an interesting finding was that although the power of alpha oscillations during rest was similar in both groups, the alpha ERD was significantly different between them. The alpha oscillations are generated by a complex cortico-thalamic network [1], [2]. Our results suggest that the modulation of alpha oscillations is a process that requires the motor cortex, as the damage in this area led to significantly reduced ERD. Still, separating the patients according to the presence or absence of damage in the motor cortex is a rough preliminary approximation to study the role of lesion location in the magnitude and modulation of alpha oscillations. The high variability among patients in the specific areas damaged by the stroke obstructs understanding the role of each segment of the circuit in shaping the alpha rhythm. Further research with more patients may allow unveiling the relationship between stroke location and alpha changes.

In a previous study, we analyzed the ERD patterns of a subset of these patients when they were controlling a robotic exoskeleton with a BMI. In that case, the ERD was not significantly different between patients with subcortical and mixed lesions [15]. A possible explanation for such result might be that the patients were receiving afferent sensory information due to the movement of the robot, which can also affect the alpha ERD [16]. One practical consequence of the difference between ERD patterns in patients with different types of stroke is that these BMI systems have a worse performance for patients with lower activity, as we have shown in a previous study [17]. This advocates for the personalization of the technologies and therapies in order to maximize their rehabilitative potential [11].

The relationship observed between resting-state activity and activity during movement attempt was specific of alpha oscillations, not appearing for delta, theta and beta

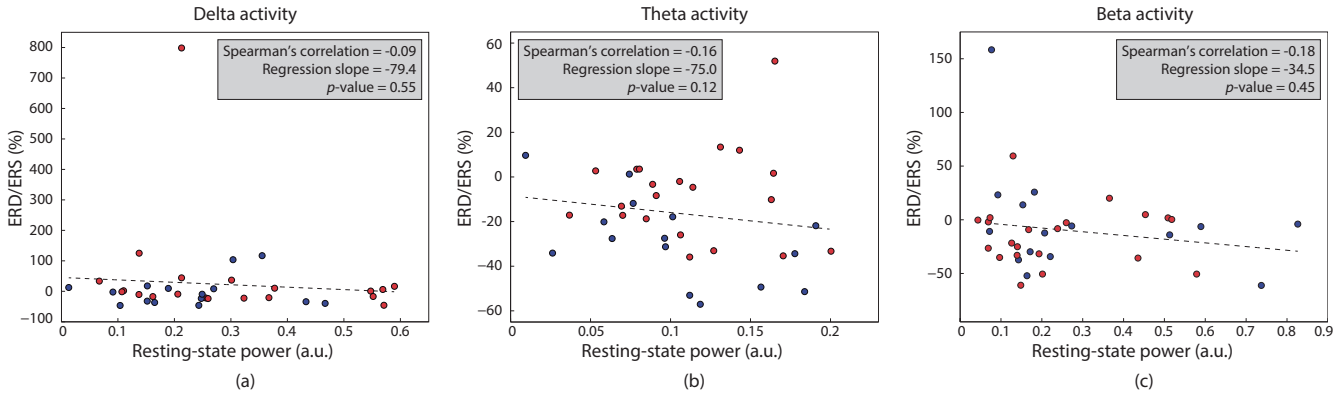

Fig. 3. Correlation analysis between resting-state and ERD/ERS activity in delta (a), theta (b) and beta (c) frequency bands. Note that different x and y axes have been used in the three subplots to facilitate visibility. The same color code than in the previous figures was used here (blue = subcortical stroke; red = mixed stroke).

frequencies. It has been recently shown that tonic alpha activity can be trained and enhanced by EEG neurofeedback, resulting in a subsequent increase of ERD [9]. The alpha rhythm is relevant in sensory and motor integration, and recent studies have shown its relationship with movement recovery in patients with stroke and spinal cord injury [18], [19]. Therefore, we believe that further research on the dynamics of this rhythm may be helpful to understand the brain changes accompanying motor paralysis and potential future therapies to improve current rehabilitation approaches.

ACKNOWLEDGMENT

The authors thank all the people involved in the data recording for their hard work. This study was funded by the Fortüne-Program of the University of Tübingen (2422-0-1 and 2452-0-0), the Bundesministerium für Bildung und Forschung, BMBF: MOTORBIC (FKZ 13GW0053) and AMORSA (FKZ 16SV7754), and Gipuzkoa Provincial Government Science Network (INKRA-TEK: OF 215/2016).

REFERENCES

[1] W. Klimesch, P. Sauseng, and S. Hanslmayr, "EEG alpha oscillations: The inhibitiontiming hypothesis," *Brain Research Reviews*, vol. 53, no. 1, pp. 63–88, 2007.

[2] W. Klimesch, "Alpha-band oscillations, attention, and controlled access to stored information," *Trends in Cognitive Sciences*, vol. 16, no. 12, pp. 606–617, 2012.

[3] G. Pfurtscheller and F. H. Lopes da Silva, "Event-related EEG/MEG synchronization and desynchronization: basic principles." *Clinical neurophysiology*, vol. 110, no. 11, pp. 1842–1857, 1999.

[4] O. Jensen and A. Mazaheri, "Shaping Functional Architecture by Oscillatory Alpha Activity: Gating by Inhibition," *Frontiers in Human Neuroscience*, vol. 4, p. 186, 2010.

[5] L. Ai and T. Ro, "The phase of prestimulus alpha oscillations affects tactile perception," *Journal of Neurophysiology*, vol. 111, no. 6, pp. 1300–1307, 2014.

[6] P. Ritter, M. Moosmann, and A. Villringer, "Rolandic alpha and beta EEG rhythms' strengths are inversely related to fMRI-BOLD signal in primary somatosensory and motor cortex." *Human brain mapping*, vol. 30, no. 4, pp. 1168–1187, 2009.

[7] B. Blankertz, C. Sannelli, S. Halder, E. M. Hammer, A. Kübler, K. R. Müller, G. Curio, and T. Dickhaus, "Neurophysiological predictor of SMR-based BCI performance," *NeuroImage*, vol. 51, no. 4, pp. 1303–1309, 2010.

[8] C. L. Maeder, C. Sannelli, S. Haufe, and B. Blankertz, "Pre-stimulus sensorimotor rhythms influence brain-computer interface classification performance." *IEEE Transactions on neural systems and rehabilitation engineering*, vol. 20, no. 5, pp. 653–662, 2012.

[9] E. López-Larraz, C. Escolano, L. Montesano, and J. Minguez, "Reactivating the Dormant Motor Cortex After Spinal Cord Injury With EEG Neurofeedback: A Case Study With a Chronic, Complete C4 Patient," *Clinical EEG and Neuroscience*, vol. In press, 2018.

[10] T. H. Murphy and D. Corbett, "Plasticity during stroke recovery: from synapse to behaviour," *Nature Reviews Neuroscience*, vol. 10, no. 12, pp. 861–872, 2009.

[11] E. López-Larraz, A. Sarasola-Sanz, N. Irastorza-Landa, N. Birbaumer, and A. Ramos-Murguialday, "Brain-machine interfaces for rehabilitation in stroke: a review," *NeuroRehabilitation*, vol. 43, no. 1, pp. 77–97, 2018.

[12] U. Chaudhary, N. Birbaumer, and A. Ramos-Murguialday, "Brain-computer interfaces for communication and rehabilitation," *Nature Reviews Neurology*, vol. 12, no. 9, pp. 513–525, 2016.

[13] A. Ramos-Murguialday, D. Broetz, M. Rea, L. Läer, O. Yilmaz, F. L. Brasil, G. Liberati, M. R. Curado, E. Garcia-Cossio, A. Vyziotis, W. Cho, M. Agostini, E. Soares, S. Soekadar, A. Caria, L. G. Cohen, and N. Birbaumer, "Brain-machine interface in chronic stroke rehabilitation: a controlled study." *Annals of neurology*, vol. 74, no. 1, pp. 100–108, 2013.

[14] E. López-Larraz, T. C. Figueiredo, A. Insausti-Delgado, U. Ziemann, N. Birbaumer, and A. Ramos-Murguialday, "Event-related desynchronization during movement attempt and execution in severely paralyzed stroke patients: an artifact removal relevance analysis," *NeuroImage: Clinical*, vol. 20, pp. 972–986, 2018.

[15] A. M. Ray, E. López-Larraz, T. C. Figueiredo, N. Birbaumer, and A. Ramos-Murguialday, "Movement-related brain oscillations vary with lesion location in severely paralyzed chronic stroke patients," in *39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2017, pp. 1664–1667.

[16] A. Ramos-Murguialday and N. Birbaumer, "Brain oscillatory signatures of motor tasks," *Journal of neurophysiology*, vol. 113, no. 10, pp. 3663–3682, 2015.

[17] E. López-Larraz, A. M. Ray, T. C. Figueiredo, C. Bibián, N. Birbaumer, and A. Ramos-Murguialday, "Stroke lesion location influences the decoding of movement intention from EEG," in *39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2017, pp. 3065–3068.

[18] C. Tangwiriyasakul, R. Verhagen, W. L. C. Rutten, and M. J. A. M. van Putten, "Temporal evolution of event-related desynchronization in acute stroke: a pilot study." *Clinical neurophysiology*, vol. 125, no. 6, pp. 1112–1120, 2014.

[19] E. López-Larraz, L. Montesano, Á. Gil-Agudo, J. Minguez, and A. Oliviero, "Evolution of EEG motor rhythms after spinal cord injury: a longitudinal study," *PLoS ONE*, vol. 10, no. 7, p. e0131759, 2015.