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Running Title : Biofeedback and Functional connectivity

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ABSTRACT

Skin Conductance Biofeedback (SCB) is a non-invasive behavioral treatment for epilepsy based on modulation of Galvanic Skin Response (GSR). We evaluated changes in functional connectivity occurring after SCB. Six patients with drug-resistant temporal lobe epilepsy underwent monthly SCB sessions. For each patient, 10 minutes of resting-state magnetoencephalographic (MEG) recording were acquired before and after the first and the last SCB session. For each recording we computed the mean weighted phase lag index (WPLI) across all pair of MEG sensors. After SCB, two patients had consistent reduction of seizure frequency (>50%). Connectivity analysis revealed a decrease of WPLI-beta band in the two responders and an increase of WPLI-alpha connectivity in all patients regardless of the clinical effect.

Results suggest that reduction of WPLI-beta-low connectivity is related to the clinical response after SCB.

Key words: Biofeedback, Epilepsy, Magnetoencephalography, Connectivity, Phase-Lag-Index.

Abbreviations: SCB= Skin Conductance Biofeedback; GSR= Galvanic Skin Response; SC= Skin Conductance; MEG= Magnetoencephalography; WPLI= weight phase lag index; CNV= Contingent Negative Variation; TLE= Temporal Lobe Epilepsy; MRI= Magnetic Resonance Imaging; EEG= Electroencephalography; CI= Confident Interval; Fc= Functional connectivity

Highlights

- Skin Conductance Biofeedback is an effective non-invasive treatment for drug-resistant epilepsy
- Only responders patients had a decrease of MEG WPLI-beta-low value after Biofeedback
- MEG WPLI-connectivity could represent a more specific index to assess biofeedback effectiveness

1. INTRODUCTION

Despite the development of new antiepileptic drugs and optimal pharmacological treatment, up to 30% of epileptic patients are drug-resistant (Janmohamed M et al, 2020).Surgical approach, cortical or deep brain stimulation, vagal nerve stimulation are some of therapeutic solutions for this population. Most of these techniques consist in invasive procedures with intrinsic surgical risk. Skin Conductance Biofeedback (SCB) based on the voluntary increase of Galvanic Skin Response (GSR) is an alternative therapy for drug-resistant epilepsy(Nagai, 2011) .Two previous studies have shown a mean reduction of seizure frequency of 48% (Kotwas et al., 2018; Nagai et al., 2004). The physiologic effect of SCB on brain cortex is not well known and is thought to originate from the concomitant variation of slow cortical potentials, another target of neuro-biofeedback treatment (Nagai et al, 2004). In particular it has been shown that cortical Contingent Negative Variation (CNV) amplitude, an index of cortical excitability imposed to the cortex by thalamic and midbrain projections (Birbaumer et al. 1990), was inversely correlated to the level of sympathetic arousal modulated through galvanic skin response(Nagai, 2011). Other case-control fMRI study investigated which cerebral systems are influenced by GSR, and found increased functional connectivity of limbic structure; in particular the greatest seizure frequency reduction was associated to the greatest increase in functional connectivity between the right amygdala and the orbitofrontal cortex(Nagai et al., 2018).

Magnetoencephalography (MEG) is a robust technique allowing the recording of magnetic fields generated by neurons. Its high temporal and spatial resolutions make it suitable to assess the functional connectivity (Fc) between different cortical areas (Liuzzi et al. 2017). The aim of our study was to investigate the effect of SCB on MEG resting state networks Fc, in order to describe a possible functional cortical rearrangement after SCB treatment. We also aimed to elucidate the mechanisms related to therapeutic response and to find specific predictors of therapeutic effect.

2. METHODS

2.2. Patients

Six patients with drug-resistant temporal lobe epilepsy (see details in supplementary material Table) were studied between January and March 2017. Mean age at the time of the study was $38\pm 8,3$ years and mean age at seizures onset was $16\pm 9,7$ years. All patients had temporal lobe epilepsy (TLE), five out of six patients describe an aura before their seizure. MRI disclosed anomalies in four patients. Participants gave informed consent. This study was conducted in accordance with the Declaration of Helsinki and French good clinical practices. There was no change in medical treatment during the study.

2.3. Biofeedback sessions

A biofeedback system (Biograph, Thought Technology Ltd., Montreal, Quebec, Canada) was used to measure and record skin conductance. During sessions, patients were instructed to enhance skin conductance activity (see details in (Kotwas et al., 2018)).

All patients performed at least 13 SCB sessions of 17 minutes each during 2-months and a half. Except for the first and last session, each subject performed multiple SCB sessions in the same day (3 to 4 per day) twice a week with a minimum interval of 2 days between them.

2.4. MEG recordings and analysis of connectivity

For each patient, 10 minutes of resting state MEG recording with 248-channels magnetometer system, sampled at 2034.51 Hz (Timone, France, 4D Neuroimaging™ 3600 whole head system) was performed before and after the first and the last SCB session, for a total of 4 recordings for each patient (these recordings will be referred as Prerun1 and Postrun1 for the first session and Prerun 2 and Postrun 2 for the last session).

Preprocessing of MEG traces was performed using the software AnyWave (Colombet et al., 2015). Cardiac and eye movement artefacts were eliminated using independent component analysis calculated on band-pass filtered signals between 1 and 100 Hz. Functional connectivity of the resting state networks was assessed at the sensor level. To reduce the dimension of the data to be analyzed and because nearby sensors are very likely to pick up activity from the same cortical sources, we down-sampled to 53 the number of MEG

sensors considered for the analysis. Those sensors were equally distributed on the total coverage of the MEG system. For the following analysis, we used the MATLAB toolbox Fieldtrip(Oostenveld et al., 2011). For each pair of MEG sensors, we computed the debiased weighted Phase Lag Index (WPLI) a non-linear estimation of the instantaneous phase differences between different cortical signals(Stam et al., 2007). Continuous artefact-free time series were segmented into two-second long segments and were tapered using a set of discrete prolate spheroidal sequences. The auto-spectra and the cross-spectra were computed using the multi-taper method(Mitra and Pesaran, 1999) and the WPLI was calculated between each pair of MEG sensors using the Fieldtrip toolbox. Differently from PLI, in WPLI the contribution of the observed phase leads and lags is weighted by the magnitude of the imaginary component of the cross-spectrum (Vinck et al., 2011). WPLI (1-100 Hz) was computed between each sensor and all the possible pair of MEG sensors. Subsequently a sub band analysis in alpha (8-12 Hz), beta low (13-25 Hz), beta high (26-35), gamma low (36-45 Hz) and gamma high (55-90 Hz) was performed. Per patient, for a given sensor, we obtained one WPLI score by averaging the WPLI values across the paired sensors, per frequency band and per recording (Prerun1 and Postrun1 for the first session and Prerun 2 and Postrun 2 for the last session).

2.5. Statistical Analysis

Paired t-tests were performed to assess any significant difference between pre-treatment (Prerun 1-2) and post-treatment (Postrun 1-2) in broadband and sub-bands WPLI value over all sensors. For an overall significance threshold of 0.01, a Bonferroni correction was used due to the multiple comparisons (15 univariate test, corrected threshold $p < 0.0006$). An ANOVA test was used to assess any significant difference in sub-bands PLI value among the runs depending on patients' clinical response and skin conductivity values.

3. RESULTS

A mean of 15 biofeedback sessions was performed in each of the 6 patients. Two patients were responders, reporting a reduction of seizure frequency >50% (patients 2 and 5). All patient (except patient 3) had a mean significant increase of skin conductance level along the sessions, the responder patients showing the higher increase of mean skin conductance value (Supplementary Fig. 1).

The WPLI values over all sensors, were compared in 6 patients between 12 post-treatment recordings (6 Post-runs 1 and 6 Post-runs 2) and 12 pre-treatment recordings (6 Pre-runs 1 and 6 Pre-runs 2), across 12 biofeedback sessions. No significant changes were observed in broadband WPLI values after SCB treatment. We observed a significant increase of WPLI-alpha after SCB treatment (mean of the differences (post – pre)= 0.011, CI 95%=[0.009, 0.014], t=8.44, p < 0.0006) a slight increase in WPLI-beta low (mean of the differences= 0.004, CI 95%=[0.002, 0.006], t=3.89, p < 0.0006) and a slight decrease of WPLI-gamma low (mean of the differences= -0.005, CI 95%=[-0.007, -0.004], t=-6.82, p < 0.0006) (Table 1). Changes of sub-bands WPLI values according to the clinical response is shown in Fig 1: the WPLI beta-low values over all sensors decreased only in good responders (mean of the differences= -0.011, CI 95%=[-0.013, -0.009], t=-9.18, p < 0.0006) after SCB treatment, while the WPLI beta-low values tended to increase in non-responders (mean of the differences= 0.011, CI 95%=[0.009, 0.014], t=9.07, p < 0.0006). Difference in WPLI beta-low values, both for good responders and for non-responders, were more pronounced in run 2 with respect to run 1 (Fig 2). In contrast WPLI-alpha over all sensors increased both in good (mean of differences (post – pre)=0.009, CI 95%=[0.005, 0.012] p < 0.0006) and non-responders (mean= 0.012, CI 95%=[0.009, 0.016] p < 0.0006) after SCB treatment in both runs (Fig 1).

ANOVA analysis showed a significant effect of response in WPLI beta-low values (-0.02 [-0.026, -0.019] p<0.0006) and run (0.009 [0.005, 0.012] p<0.0006) with a significant interaction between these two factors (p<0.0006) on the differences postrun-prerun. In WPLI-alpha, the response seemed to have no effect (response: -0.004 [-0.009, 0.002] p=0.176, run: 0.010 [0.005, 0.015] p<0.0006) but significant interaction between response and run was observed (p<0.0006). In the two bands, Tuckey's post-hoc test showed that the differences (post-pre) in the two runs were significant only for the non-responders (WPLI alpha: responders: -0.006 [-0.018, 0.005] p=0.52; non-responders: 0.018 [0.01, 0.026] p<0.0006. WPLI beta-low band: responders: -0.007 [-0.015, 0.001] p=0.126; non-responders: 0.017 [0.010, 0.022] p<0.0006).

4. DISCUSSION

We observed a reduction in WPLI-low-beta band connectivity after SCB in good responder patients. The beta band is an important frequency band for cognition and motor processes; its activity usually increases during consciousness activity, alertness, motor preparation and mental activation(Engel and Fries, 2010).

Taking into account that the effect of biofeedback is thought to arise from its ability to increase epileptogenic threshold of the brain (Nagai, 2011; Walker and Kozlowski, 2005), we could speculate that biofeedback acts by reducing large scale cortical-subcortical synchronization especially in beta band.

The present study also found an increase in WPLI-alpha connectivity in all patients irrespectively of clinical impact that could be interpreted as a non-specific effect of the biofeedback intervention. This effect is possibly linked to the increase of patient's attentional level that is required during the SCB session. The lack of specific role of WPLI-alpha increase on SCB effectiveness observed in the present study is in line with other neurofeedback protocols in epilepsy aiming to reduce theta/alpha power ratio and increase sensory-motor rhythms (11-15 Hz) (Marzbani et al., 2016).

Concerning skin conductance changes during SCB, we found that all patients except one had a significant increase of skin conductance value among biofeedback sessions, in line with previous studies (Kotwas et al., 2018; Nagai et al., 2004). However, considering only the first and last session of biofeedback, during which MEG recording were acquired, we did not find a strict correlation between skin conductance difference and clinical response. On the contrary WPLI-beta-low difference displayed an opposite change in responder and non-responder patients, which was already evident in the first run and tended to increase in the second run.

Thus, decreased PLI-beta-low could be a better predictor of clinical effect. **Our study suggests that biofeedback is likely to modify the physiology of cerebral networks. This has been shown in only one fMRI study to date, where biofeedback in responders has increased the connections between the amygdala and the orbitofrontal cortex (Nagai et al, 2011). Interestingly, it has been shown that the decrease in synchrony observed in EEG scalp is predictive of the therapeutic response of VNS treatment (Bartolomei et al, 2016; Sangare et al, 2020). Thus a common mechanism of brain modulation techniques could be a reduction in brain synchrony that is increased in the epileptogenic zone of focal epilepsy (Lagarde et al, 2018).**

Due to the small sample size of our cohort we cannot draw definitive results nor specific hypotheses on the mechanisms by which SCB could modulate beta band connectivity and epileptogenic threshold. Further investigations are needed in larger cohorts in order to confirm these preliminary results.

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Legends of Tables and Figures

Table 1: Mean weighted Phase Lag Index (WPLI) postrun-prerun differences across biofeedback sessions for each run and frequency band with 95% confidence interval(CI) and t-test p-value. *=significant difference

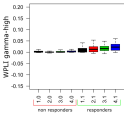
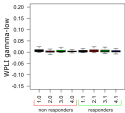
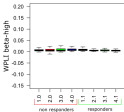
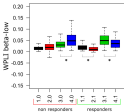
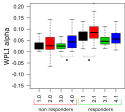
Figure 1: Mean weighted Phase Lag Index (WPLI) values among runs. 1.0 to 4.0: trends in non-responders; 1.1 to 4.1: trends in responders' patients. Note the decrease in beta low WPLI values between pre-and post-run that is specific to responder patients

Abbreviations: 1.0= prerun1 of non-responders; 2.0 postrun1 of non-responders; 3.0 prerun2 of non-responders; 4.0 postrun2 of non-responders. 1.1= prerun1 of responders; 2.1 postrun1 of responders; 3.1 prerun2 of responders; 4.1 postrun2 of responders.

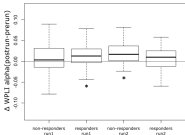
Figure 2: WPLI-alpha differences after biofeedback treatment (post-pre) is displayed on left side according to clinical response (responders, non-responder) and run (run1, run2). WPLI-beta low difference after biofeedback treatment is displayed in right side according to clinical response and run. Lower table reports the mean difference WPLI postrun-prerun according to run and clinical response (with CI 95% and t-test p-value).

Disclosure

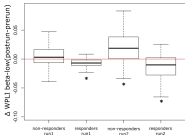
“None of the authors has any conflict of interest to disclose.”



Difference WPLI alpha postrun-prerun according to clinical response



Difference WPLI beta-low postrun-prerun according to clinical response



		WPLI alpha	WPLI beta-low
Non-responders	run1	0.003 [-0.002, 0.009] p=0.246	0.003 [-0.00003, 0.007] p=0.052
	run2	0.021 [0.018, 0.025] p<0.0006	0.020 [0.016, 0.023] p<0.0006
	run1+run2	0.012 [0.009, 0.016] p<0.0006	0.012 [0.009, 0.014] p<0.0006
Responders	run1	0.012 [0.007, 0.017] p<0.0006	-0.007 [-0.009, -0.006] p<0.0006
	run2	0.006 [0.0005, 0.011] p=0.033	-0.014 [-0.019, -0.010] p<0.0006
	run1+run2	0.009 [0.005, 0.012] p<0.0006	-0.011 [-0.013, -0.009] p<0.0006

Table 2

	Alpha	Beta Low	Beta High	Gamma Low	Gamma High
RUN 1	0.006 [0.002,0.01] (p=0.003)	-0.0004 [-0.003,0.002] (p=0.75)	-0.003 [-0.0045,-0.001] (p=0.002)	-0.006* [-0.008,-0.003] (p=1.2e-05)	-0.006* [-0.009,-0.003] (p=7.2e-05)
RUN 2	0.016* [0.013, 0.019] (p<2.2e-16)	0.008* [0.005, 0.012] (p=6.6e-07)	-0.0007 [-0.002, 0.0005] (p=0.256)	-0.005* [-0.006, -0.003] (p=1.5e-08)	0.002 [0.0002, 0.003] (p=0.03)
RUN1+RUN2	0.011* [0.009, 0.014] (p<2.2e-16)	0.004* [0.002, 0.006] (p=0.0002)	-0.002 [-0.003,-0.0007] (p=0.002)	-0.005* [-0.007,-0.004] (p=2.1e-11)	-0.002 [-0.004,-0.0006] (p=0.009)