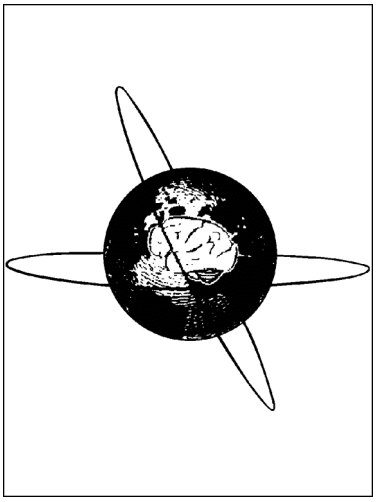
Accepted Manuscript



Modulation of critical brain dynamics using closed-loop neurofeedback stimulation

Alexander Zhigalov, Alexander Kaplan, J. Matias Palva

PII: S1388-2457(16)30057-8
DOI: http://dx.doi.org/10.1016/j.clinph.2016.04.028
Reference: CLINPH 2007830

To appear in: *Clinical Neurophysiology*

Accepted Date: 30 April 2016

Please cite this article as: Zhigalov, A., Kaplan, A., Matias Palva, J., Modulation of critical brain dynamics using closed-loop neurofeedback stimulation, *Clinical Neurophysiology* (2016), doi: http://dx.doi.org/10.1016/j.clinph.2016.04.028

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Modulation of critical brain dynamics using closed-loop neurofeedback stimulation

Alexander Zhigalov[1,2*], Alexander Kaplan[2], J. Matias Palva[1]

[1]Neuroscience Center, University of Helsinki, Helsinki 00014, Finland

[2]Laboratory for Neurophysiology and Neuro-Computer Interfaces, Faculty of Biology, Lomonosov Moscow State University, Moscow 119991, Russia

Corresponding author:

A. Zhigalov

Neuroscience Center, University of Helsinki, Helsinki 00014, Finland

Tel.: +358 50 448 4738

Fax: +358 91 915 7620

E-mail: alexander.zhigalov@helsinki.fi

Keywords: Closed-loop stimulation; electroencephalography; critical neuronal dynamics; long-range temporal correlations; excitation-inhibition balance.

Highlights

- We examined whether closed-loop neurofeedback stimulation could be used to alter α-rhythm oscillation dynamics.
- Closed-loop stimulation suppressed EEG long-range temporal correlations (LRTCs) and evoked responses without changing the power spectrum.
- A possibility to influence LRTCs automatically opens new avenues for examining the functional role of criticality in the brain and developing novel therapeutic tools for brain disorders.

Abstract

Objective: EEG long-range temporal correlations (LRTCs) are a significant for both human cognition and brain disorders, but beyond suppression by sensory disruption, there are little means for influencing them non-invasively. We hypothesized that LRTCs could be controlled by engaging intrinsic neuroregulation through closed-loop neurofeedback stimulation.

Methods: We used a closed-loop-stimulation paradigm where supra-threshold α-waves trigger visual flash stimuli while the subject performs the standard eyes-closed resting-state task. As a "sham" control condition, we applied similar stimulus sequences without the neurofeedback.

ACCEPTED MANUSCRIPT

Results: Over three sessions, a significant difference in the LRTCs of α-band oscillations (U = 89, $p < 0.028$, *Wilcoxon rank sum test*) and their scalp topography (T = -2.92, $p < 0.010$, *T-test*) emerged between the neurofeedback and sham conditions so that the LRTCs were stronger during neurofeedback than sham. No changes (F = 0.16, $p > 0.69$, *ANOVA test*) in the scalp topography of α-band power were observed in either condition.

Conclusions: This study provides proof-of-concept for that EEG LRTCs, and hence critical brain dynamics, can be modulated with closed-loop stimulation in an automatic, involuntary fashion. We suggest that this modulation is mediated by an excitation-inhibition balance change achieved by the closed-loop neuroregulation.

Significance: Automatic LRTC modulation opens novel avenues for both examining the functional roles of brain criticality in healthy subjects and for developing novel therapeutic approaches for brain disorders associated with abnormal LRTCs.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

1. Introduction

Several lines of electrophysiological (Linkenkaer-Hansen, et al. 2001), blood-oxygenation-level dependent (BOLD) signal imaging (Bullmore, et al. 2004) and behavioral (Gilden, et al. 1995,Palva, et al. 2013) evidence show that many features of central-nervous system activity *in vivo* are scale-free. The absence of specific scale (scale free) is a common attribute of self-similar processes or objects meaning that their properties remain similar at any scale (Hardstone, et al. 2012). Scale-free dynamics is relevant because it is a signature characteristic of complex systems poised at criticality (Chialvo. 2010). Operating at a critical state endows the system maximal dynamic range (Shew, et al. 2009,Kinouchi and Copelli. 2006) and optimal information storage and transmission capacity (Shew, et al. 2011). Scale-free dynamics of a near-critical complex system can be quantitatively described by the corresponding power-law scaling exponents of long-range temporal correlations (LRTCs) (Bak, et al. 1987). These exponents reflect the decay of autocorrelations and when estimated with detrended fluctuation analysis (DFA), range from 0.5 to ~1, where 0.5 indicates a temporally uncorrelated time series. The scaling exponents of LRTCs are both predictive of behavioral dynamics (Palva, et al. 2013,Smit, et al. 2013) and robust biomarkers for many brain diseases (Linkenkaer-Hansen, et al. 2005,Montez, et al. 2009,Nikulin, et al. 2012). LRTCs characterize the amplitude envelopes of neuronal oscillations in human magneto- (MEG) and electroencephalography (EEG) (Linkenkaer-Hansen, et al. 2001) as well as in intracranial recordings (Monto, et al. 2007,Zhigalov, et al. 2015).

Discovering means to influence brain criticality would be important for both examining its functional role in cognition and for developing novel therapeutic approaches for brain disorders associated with abnormal LRTCs. It has been suggested that the net balance between excitation and inhibition is the control parameter that tunes the brains to operate in the critical regime (Shew, et al. 2009,Beggs and Timme. 2012) and to avoid the sub-critical and super-critical states that are associated with aberrant levels of neuronal inhibition and excitation, respectively. Here we advance a closed-loop neurofeedback stimulation paradigm that may modulate the excitation/inhibition (E/I) balance and the LRTCs. Neurofeedback technologies have attracted growing interest from different fields of research and have found applications, *e.g.*, in the treatment of brain disorders such as the attention-deficit hyperactivity disorder (Arns, et al. 2009), epilepsy (Strehl, et al. 2014), and depression (Linden. 2014) as well as in helping people with severe neuromuscular disorders (Wolpaw, et al. 2002). Neurofeedback-based brain-computer interfaces (BCI) have also gained popularity in digital entertainment and video gaming (Kaplan, et al. 2013). Nevertheless, neurofeedback has not been widely acknowledged as a research tool for cognitive neuroscience because of technical and conceptual difficulties (Jensen, et al. 2011).

Numerous studies have focused on α-rhythm- (8–12 Hz) based neuro-feedback (for review, (Gruzelier. 2014a)). The goal of "α-training" is an intentional and voluntary modulation of amplitude of neuronal oscillations through operant conditioning (Kamiya. 1968). An intentional increase of α-power leads to diverse cognitive improvements such as enhanced performance in a mental rotation task (Zoefel, et al. 2011) and working memory

ACCEPTED MANUSCRIPT

capacity in a conceptual span test (Escolano, et al. 2011). α-neurofeedback also promotes other cognitive and affective benefits such as improved sustained attention, reaction time, intelligence, and mood (Gruzelier. 2014a), which indicates that neurofeedback can tap into functionally significant neuronal processing. Also human perceptual performance can be enhanced endogenously by neurofeedback modulation of neuronal activity in retinotopically specific regions of the visual cortex (Scharnowski, et al. 2012). However, comparable effects can also by achieved exogenously through rhythmic visual (Mathewson, et al. 2012) and transcranial magnetic (Romei, et al. 2012) stimulation (TMS).

Changes in neuronal activity caused by neurofeedback training are likely associated with systematic shifts in the cortical E/I balance as shown, *e.g.*, by cortico-spinal excitability measurements (Ros, et al. 2010,Studer, et al. 2014,Ros, et al. 2014). In particular, voluntary suppression of α-activity increases the cortico-spinal excitability and decreases the intra-cortical inhibition (Ros, et al. 2010), which shows that cortical E/I balance can be directly modulated via neurofeedback. However, to achieve such E/I shifts during cognitive tasks or in clinical applications (Ros, et al. 2014), automatic means for E/I modulation would be preferable over voluntary and cognitive-effort demanding methods. Closed-loop stimulation is a neurofeedback paradigm that combines the endo- and exogenous approaches so that specific aspects of neuronal activity as used to trigger sensory stimuli that then reciprocally influence the ongoing neuronal activity.

In this study, we developed a closed-loop stimulation paradigm where high-amplitude α-waves trigger visual flash stimuli during an eyes-closed resting condition. The stimulation threshold allows intrinsic neuroregulation to control the stimulation rate through α-wave amplitude adjustment. Given the direct link of α-oscillations and excitability (Wang. 2010), such adjustments are associated with shifts in the E/I balance. Moreover, because the subjects are not informed about the connection between ongoing neuronal activity and the visual stimuli, the paradigm assesses specifically the effects of endogenous adaptive mechanisms (Kaplan, et al. 2005,Batty, et al. 2006). We hence hypothesized that the closed-loop stimulation changes LRTCs, which would imply a change in the operating point of brain dynamics along the sub-/super-critical axis. We tested the hypothesis by measuring the scaling exponents of EEG LRTCs during the neurofeedback (closed loop) and sham (disconnected loop) conditions.

2. Methods

2.1. Participants

Nine healthy subjects (age of 18-23 years old, four female) participated in the study. This study was approved by the Ethical Committee of the Department of Physiology of Moscow State University and was performed according to the Declaration of Helsinki. All participants gave written informed consent. Prior EEG screening revealed a pronounced alpha rhythm in EEG of all participants.

ACCEPTED MANUSCRIPT

2.2. Experimental design and equipment

The participants were instructed to relax and keep their eyes closed during the experiments. Importantly, the participants were not informed about the fact that their brain activity influences the appearance of the stimuli, in order to perform unconscious or automatic neurofeedback closed-loop stimulation.

Neurofeedback and sham stimulation sessions were carried out in two separate days. In both sessions, brain activity was recorded at 500 Hz from eight EEG electrodes positioned according to the 10-20 systems with nasion reference (Fig. 1A).

In the neurofeedback session, EEG activity from the right occipital channel (Fig. 1A) was filtered in real-time using forth order narrowband IIR filter (8–12 Hz) and the peaks of supra-threshold α-waves were detected (Fig. 1A). The threshold was adjusted individually for each subject prior to the experiment, in a manner that at least ten α-waves with amplitude above the threshold occur during twenty seconds of recordings which ensure minimal stimulation rate of 0.5 stimuli per second. Visual flash stimuli were presented at constant latency of 12.5 ms after the peak of supra-threshold α-wave. The stimuli were produced by eight white embedded light-emitted diodes (LED; 3mm, 2.5 cd) mounted on plastic glasses on the subject's head. Brightness of the flashes was adjusted so that the flashes were visible with closed eyes and did not cause discomfort. The duration of each flash was 20 ms.

In the sham session, visual stimuli were triggered by the peaks that are detected in the neurofeedback session, and therefore, ongoing brain activity did not influence the appearance of the stimuli. The average number of stimuli was 1476 (± 472) that roughly corresponded to the stimulation rate of 1.2 (± 0.4) stimuli per second.

Both neurofeedback and sham conditions consisted of three sessions by 20 minutes followed by ten minutes breaks. After each session subjects were briefly interviewed on their emotional and psychophysical conditions in order to prevent negative outcome of the stimulation.

2.3. Data analysis

Closed-loop stimulation typically induces changes in power of EEG oscillations. EEG power is unequally distributed over the scalp surface depending of the frequency of underlying neuronal oscillations. Spatial distribution of power of α-oscillations has a stereotypical fronto-parietal gradient, where occipital regions show larger amplitudes than the frontal areas of the brain.

We assessed the changes in EEG power associated with closed-loop stimulation in neurofeedback and sham conditions. The power spectra were computed for each channel, session, condition and subject. The EEG time series were divided into two second non-overlapping segments and Hanning windowed to reduce the spectral

ACCEPTED MANUSCRIPT

leakage. The Fourier transform was applied to each segment and the power spectra were averaged across the segments. The power spectra were computed in the range of 3–40 Hz and had a frequency resolution of 0.5 Hz.

To investigate the changes in temporal structure of EEG we applied detrended-fluctuation analysis (DFA) (Peng, et al. 1995). Prior to the analysis, EEG time series were filtered with Morlet wavelets (shape parameter ω=5) for the logarithmically spaced central frequency from 3 to 40 Hz, and the amplitude envelopes (Fig. 1B) were used as an input time series for DFA. DFA is a two-stage procedure: in the first stage, time series $X(k)$ (Fig. 1B) is normalized to zero mean and integrated, $y(k) = \sum_{i=1}^{k}[X(i) - \langle X \rangle]$, then segmented into time windows of various sizes Δt (Fig. 1C). In the second stage, each segment of integrated data is locally fitted to a linear function $u(k)$ and the mean-squared residuals $F(\Delta t)$ are computed,

$$F(\Delta t) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}[y(k) - u(k)]^2}$$

where N is the total number of data points. The scaling exponent β is defined as the slope of linear regression of the function $F(\Delta t)$ in double logarithmic coordinates, estimated using a least-squares algorithm.
The linearity of the slope was validated using the maximum likelihood based technique (Botcharova, et al. 2013,Botcharova, et al. 2014). The optimal fitting range for the current dataset was limited to 3–300 seconds.

To assess the statistical significance of the DFA exponents without making assumptions about the theoretical distribution of data, the exponents were computed for phase-shuffled data (Linkenkaer-Hansen, et al. 2001,Prichard and Theiler. 1994). Phase-shuffling disrupts temporal as well as spatial correlations in multichannel
time series while preserving the power spectrum. We repeated the phase-shuffling procedure 1000 times to estimate the confidence interval of 99.9%, corresponding to $p < 0.001$.

Statistical difference of the power spectra across sessions within and between conditions were assessed using the *Kruskal-Wallis test* that is a non-parametric alternative of *ANOVA test*. The rationale for applying the non-parametric test was that the distribution of power was not Normal ($\chi^2 = 93.45$, $p < 0.0001$, *Chi-square test*). Similarly, we compared the scaling exponents that did not follow Normal distribution ($\chi^2 = 76.41$, $p < 0.0001$, *Chi-square test*). The *Wilcoxon rank sum test* was utilized for post hoc comparisons at specific frequencies.

To evaluate changes in fronto-parietal gradient of α-band power, we first estimated the gradient (slope of linear function) of power from occipital to frontal channels, and then applied *ANOVA test* to compare these slopes across sessions within and between conditions. We ensured that the gradient was well approximated by a linear

ACCEPTED MANUSCRIPT

function (goodness-of-fit $R^2 > 0.90$) and that the slopes were Normally distributed ($\chi^2 = 3.23$, $p > 0.66$, *Chi-square test*). The fronto-parietal gradients of the α-band scaling exponents were compared in the same manner. We used the *t-test* for post hoc comparisons between certain sessions.

To assess changes in neuronal activity at fast time-scales (0.01–0.1 s), we analyzed evoked responses. The evoked responses were computed in a time window from -250 to 250 ms from the onsets of first stimuli in consecutive alpha waves. Stimuli that occurred earlier than 200 ms (approximately 2 cycles α-waves) after the first stimulus were discarded from the analysis to reduce the effect of rhythmic stimulation on the evoked response. We compared peak-to-peak amplitudes of the responses in the time window of 0–250 ms, across sessions within and between conditions using the *Kruskal-Wallis test* because the responses were far from being Normally distributed ($\chi^2 = 76.31$, $p < 0.0001$, *Chi-square test*). For *post hoc* comparisons, Wilcoxon-rank-sum test was applied.

3. Results

Closed-loop neurofeedback stimulation is known to alter brain dynamics such as the power of ongoing oscillations and their entrainment. In this study, we address the changes in spatio-temporal neuronal dynamics caused by closed-loop neurofeedback stimulation compared against a sham condition with using identical stimulation but without the feedback loop.

3.1. Power spectrum remained unchanged in neurofeedback and sham conditions

We assessed the effects of closed-loop stimulation on EEG power spectra by first inspecting the session-averaged scalp topographies in the α-frequency band power (Fig. 2A). The topography revealed a prominent fronto-parietal gradient but neither differences between the neurofeedback and sham conditions ($F = 0.16$, $p > 0.69$, *ANOVA test*) nor significant changes over the training sessions in either the neurofeedback ($F = 0.21$, $p > 0.81$, *ANOVA test*) or sham conditions ($F = 0.19$, $p > 0.83$, *ANOVA test*). We then examined the full frequency spectrum (3–40 Hz; Fig. 2B) but again found no differences between the conditions ($\chi^2 = 0.96$, $p > 0.62$, *Kruskal-Wallis test*) and not changes across sessions in the neurofeedback ($\chi^2 = 1.10$, $p > 0.58$, *Kruskal-Wallis test*) or sham ($\chi^2 = 0.25$, $p > 0.88$, *Kruskal-Wallis test*) conditions.

3.2. Neurofeedback changes the spatial distribution of α-band LRTCs over the cortex

We used the detrended fluctuation analysis (DFA) to assess the power-law scaling exponents of long-range temporal correlations (LRTCs) of amplitude envelopes of ongoing oscillations (Linkenkaer-Hansen, et al. 2001,Zhigalov, et al. 2015). In line with prior observations, we found salient power-law scaling in amplitude envelopes of α-oscillations. To address whether the stimulation affected the scaling exponents of LRTCs, we

ACCEPTED MANUSCRIPT

first examined the α-band topography (Fig. 3A). The results showed significant differences in the fronto-pariental gradient of scaling exponents between sessions in the feedback ($F = 4.51$, $p < 0.02$, *ANOVA*) but not in sham ($F = 0.92$, $p > 0.41$, *ANOVA*) conditions. We found that the fronto-parietal gradient of scalp scaling exponents decreased in the last session compared to the first ($T = -2.46$, $p < 0.027$, *T-test*) and second ($T = -2.92$, $p < 0.010$, *T-test*) sessions in the feedback condition. These findings hence suggest that closed-loop α-wave visual stimulation controlled by a single right occipital channel induces changes in the LRTC scaling exponents over large spatial distances.

3.3. LRTCs increase in α-band in neurofeedback but not in sham conditions

We then evaluated the changes of scaling exponents as a function of frequency in the range of 3–40 Hz (Fig. 3B). The scaling exponents were significantly different (well above the 99.9% confidence interval) from those of surrogate data in the entire frequency range (Fig. 3B). The results revealed attenuation of the scaling exponents in a wide range of frequencies (8–32 Hz) after the first session in the feedback ($\chi^2 = 8.48$, $p < 0.014$, *Kruskal-Wallis test*) and sham ($\chi^2 = 7.42$, $p < 0.025$, *Kruskal-Wallis test*) conditions. While both conditions shared a similar overall attenuation pattern, we found a significant difference ($U = 89$, $p < 0.028$, *Wilcoxon rank sum test*) specifically in α-frequency band scaling exponents between the neurofeedback and sham conditions in the last session. This finding strongly suggests that unlike the uncontrollable sham-condition stimuli, closed-loop stimulation is progressively associated with active albeit unconscious neuroregulation for restoring complexity in brain dynamics.

3.4. Evoke responses are progressively enhanced in by feedback but not by sham stimulation

The observations above showed that closed-loop stimulation and sham stimulation had distinct effects on 3–300 s time scale neuronal dynamics reflected in LRTCs. In order to evaluate the impact of neurofeedback on neuronal activity in sub-second time-scales, we assessed the evoked responses. The peak-to-peak amplitudes of evoked responses in the window of 0–250 ms were compared between three sessions of feedback or sham conditions using the Kruskal-Wallis test. For post hoc analysis, the amplitudes of evoked responses were compared in pairwise manner between sessions using the Wilcoxon rank sum test.

The results showed that the amplitudes of evoked responses in occipital channels were significantly different between sessions ($\chi^2 = 6.35$, $p < 0.04$, *Kruskal-Wallis test*) in feedback but not in sham ($\chi^2 = 3.41$, $p > 0.18$, *Kruskal-Wallis test*) conditions (Fig. 4). The amplitudes of responses were progressively increased over the sessions and a significant difference were observed between the first and last sessions ($U = 233$, $p < 0.03$, *Wilcoxon rank sum test*) in the feedback condition.

We found no differences in evoked responses between sessions for the parietal ($\chi^2 = 2.66$, $p > 0.27$, feedback and $\chi^2 = 1.27$, $p > 0.53$, sham), central ($\chi^2 = 0.21$, $p > 0.89$, feedback and $\chi^2 = 0.48$, $p > 0.79$, sham) or frontal ($\chi^2 =$

ACCEPTED MANUSCRIPT

0.59, $p > 0.74$, feedback and $\chi^2 = 0.64$, $p > 0.72$, sham) channels, which suggests that the effect of neurofeedback at fast time scales were localized in visual areas.

4. Discussion

In short time scales, closed-loop sensory stimulation entrains neuronal oscillations and enhances perceptual performance (Mathewson, et al. 2012). On the other hand, closed loop stimulation is also known to have long-time-scale effects such as improvements in memory performance (Ngo, et al. 2013) and alleviation of depression symptoms (Kumano, et al. 1996). Nevertheless, in the absence of a conceptual framework explaining the self-regulatory changes in brain dynamics during stimulation, the physiological basis for the effects of closed-loop stimulation has remained incompletely understood. The theory of critical brain dynamics could be useful in this context when one assumes that during closed-loop stimulation, endogenous homeostatic mechanisms may be recruited to preserve the neuronal E/I balance. It has been suggested that a healthy brain is a well-balanced complex system (Shew and Plenz. 2013) that operates near a critical point (Chialvo. 2010). Criticality may provide several functional benefits for the brain such as optimal dynamic range (Shew, et al. 2009,Kinouchi and Copelli. 2006), information transmission and information capacity (Shew, et al. 2011). The long-range temporal correlations (LRTCs) are the hallmarks of critical dynamics in the human brain (Linkenkaer-Hansen, et al. 2001). Our results show that closed-loop stimulation induces changes in LRTCs and hence in critical dynamics without changes in the global power of neuronal oscillations. Importantly, the comparison with the sham condition showed that while both conditions were characterized by overall suppressed LRTCs, which is attributable to the sensory stimuli disrupting endogenous dynamics (Linkenkaer-Hansen, et al. 2004), the effect of closed-loop stimulation was to enhance the LRTC. Because LTRCs are positively correlated with the proximity to the critical point (Poil, et al. 2012), the closed-loop stimulation thus appears to shift the brain towards to a critical state and alleviate the sensory-stimulation induced disruption in scale-free dynamics.

4.1. Changes in temporal structures of ongoing neuronal oscillations do not affect the total power

The power of the α-rhythm is correlated with cognitive and memory performance (Klimesch. 1999), and some neurofeedback training studies have shown that intentional increasing of α power enhances the cognitive functions and behavioral performance (Gruzelier. 2014a,Zoefel, et al. 2011). Importantly, the effect of training may be sustained over several months (Gruzelier. 2014b). The voluntarily induced changes in EEG power may also be accompanied by changes in the EEG spectral topography, but the effects do not necessary correspond to either frequencies or scalp locations by the training contingencies (Egner, et al. 2004), showing that the neuronal dynamics involved EEG self-regulation are complex.

In our study, the conditioning of neuronal activity picked up by an occipital EEG electrode caused changes in LRTCs in both frontal and contralateral electrodes suggesting that the LRTCs and their large-scale organization

ACCEPTED MANUSCRIPT

are more susceptible to closed-loop control than the overall power of ongoing oscillations. The results thus suggest that neuronal circuits are more capable of reorganizing their temporal dynamics than the magnitudes of activity and local synchronization. Studies using classical neurofeedback of increasing of α-power have shown that the increases in α-wave amplitudes can be observed only for brief periods of time (0.5–2 s) (Bazanova and Vernon. 2014). Thus, the maintenance of high α-power over long time periods appears demanding for the brain and long-term power changes are likely to be unfeasible, which might be related to limited resources shared among neuronal groups (Bullmore and Sporns. 2012).

4.2. Distribution of LRTCs over cortical surface changes during closed-loop stimulation

Pronounced EEG α-rhythms are typically is associated with sources in the occipito-parietal areas of the human brain. In the study we have shown that the temporal characteristics of brain activity in contrast to power can be modulated over the large cortical distances. Prior studies have shown that there is a strong correspondence between LRTCs of certain regions and behavioral performance (Palva, et al. 2013) or brain disorders (Montez, et al. 2009,Nikulin, et al. 2012). The possibility to modulate the LRTCs in specific brain regions in an involuntary, automatic fashion would provide an opportunity to obtain perturbational evidence (Massimini, et al. 2009) about the roles of specific neuronal mechanisms in cognitive functions or pathological conditions. Such neuroanatomically targeted closed-loop experiments could be achievable with magnetoencephalography and online source modelling.

4.3. Neuronal evoked responses are increases during closed-loop stimulation

Both in-phase and out-of-phase stimulation is known to affect the amplitude of evoked response (Ngo, et al. 2013,Kruglikov and Schiff. 2003). In-phase stimulation normally increases the amplitude of evoked responses while out-of-phase stimulation has the opposite effect (Ngo, et al. 2013). In this study we observed an increase of amplitude of evoked responses over the training sessions in the neurofeedback condition. This observation suggests that not only in-phase stimulation but also unconscious neuroregulation influences the amplitudes of evoked responses. This supports the notion that there is an interaction between ongoing neuronal activity and evoked responses (Scheeringa, et al. 2011,He. 2013) rather than their linear summation.

5. Conclusion

We used closed-loop neurofeedback stimulation where visual stimuli were triggered by supra-threshold α-waves. The changes in the LRTCs but not in the power of α-oscillations during the stimulation suggest that the brains prevent the global cortical excitation by preserving E/I balance. The proposed approach demonstrated the possibility for automatic modulation of LRTCs. The effect size of automatic modulation was smaller than that attributable to the disruptive effects of the visual stimuli per se, but prolonged stimulation as well as using more

ACCEPTED MANUSCRIPT

subtle, lower intensity stimuli could both increase the effect and decrease the stimulation related disruption of cortical dynamics. This approach thus opens novel avenues for both examining the functional roles of brain criticality in healthy subjects and for developing novel therapeutic approaches for brain disorders associated with abnormal LRTCs.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Acknowledgements

This work was funded by Centre for International Mobility CIMO Grant TM-14-9492 (A.Z.), Academy of Finland grants 266745 and 281414 (J.M.P), and by the Skolkovo Foundation Grant 1110034, Pirogov Russian National Research Medical University and Russian Science Foundation project #15-19-20053 (A.K.).

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Figure Legends

Fig. 1. Schematic representation of the closed-loop stimulation paradigm and data analysis pipeline. (A) EEG activity from right occipital electrode (*black line*) filtered in real time using a narrow-band IIR filter (*gray line*). Alpha wave peaks exceeding the threshold (*green line*) triggered brief flashes of light (*red dots*) in LED glasses. (B) Flowchart of the detrended fluctuation analysis (DFA) for estimating the scaling exponent of long-range temporal correlations (LRTCs). The amplitude envelope (*black line*) of narrowband filtered EEG signal (*gray line*) is integrated (*orange line*) and (C) locally fitted for multiple time windows (*blue line*) using root-mean square approach. (D) The root-mean square errors for each time window (Δt) are plotted in double logarithmic coordinates and approximated by a linear function with a slope β that is the LRTC scaling exponent.

Fig. 2. Average EEG power remains unchanged in the feedback and sham conditions. (A) α-band power remains stable during α-wave triggered visual stimulation in the feedback (*blue circle*) and sham (*red circle*) conditions over the sessions and was not different between the conditions. (B) The power spectrum in the frequency range of 3–40 Hz remains unchanged in the feedback (*blue lines*) and sham (*red lines*) conditions across sessions and was not different between the conditions. Error bars indicate the standard error of mean across channels (*SEM*).

Fig. 3. The scalp topography and magnitude of LRTC scaling exponents can be modulated in a narrow frequency band via neurofeedback. (A) Scaling exponents are attenuated by the α-wave closed-loop visual stimulation in both feedback (*blue circle*) and sham (*red circle*) conditions over the sessions. A fronto-parietal gradient of the scaling exponents changes over the sessions and shows a remarkable decrease in the last session of neurofeedback condition (T = -2.46, $p < 0.027$, *T-test*) so that the feedback-related enhancement of LRTC scaling exponents was relatively most pronounced at frontal EEG contacts. (B) An overall attenuation of scaling exponents in a wide range of 8–32 Hz after the first session in both neurofeedback (*blue lines*) and sham (*red lines*) sessions is likely attributable to stimulus-induced suppression of critical dynamics (Linkenkaer-Hansen, et al. 2004). The α-band LRTC scaling exponents in the last session of neurofeedback condition were, however, greater than in the sham condition and their variability was smaller (U=89, $p < 0.028$, *Wilcoxon rank sum test*). The scaling exponents in the feedback and sham conditions were well above 99.9% confidence limits compared to the exponents of surrogate data (*shaded area*).

Fig. 4. Evoked responses became enhanced in magnitude across the sessions in the neurofeedback but not sham condition. The amplitudes of evoked responses for the first (*blue line*), second (*green line*), and third (*orange line*) session are shown for four channels of right hemisphere. The significant differences between the first and last sessions in feedback condition are indicated by black horizontal line (*$p < 0.05$).

ACCEPTED MANUSCRIPT

References

Arns M, de Ridder S, Strehl U, Breteler M, Coenen A. Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. Clin.EEG Neurosci. 2009;40:180-189.

Bak P, Tang C, Wiesenfeld K. Self-organized criticality: An explanation of the 1/f noise. Phys.Rev.Lett. 1987;59:381-384.

Batty MJ, Bonnington S, Tang BK, Hawken MB, Gruzelier JH. Relaxation strategies and enhancement of hypnotic susceptibility: EEG neurofeedback, progressive muscle relaxation and self-hypnosis. Brain Res.Bull. 2006;71:83-90.

Bazanova OM, Vernon D. Interpreting EEG alpha activity. Neurosci.Biobehav.Rev. 2014;44:94-110.

Beggs JM, Timme N. Being critical of criticality in the brain. Front.Physiol. 2012;3:163.

Botcharova M, Farmer S, Berthouze L. A maximum likelihood based technique for validating detrended fluctuation analysis (ML-DFA). arXiv:1306.5075 [q-bio.QM] 2013.

Botcharova M, Farmer SF, Berthouze L. Markers of criticality in phase synchronization. Front.Syst.Neurosci. 2014;8:176.

Bullmore E, Fadili J, Maxim V, Sendur L, Whitcher B, Suckling J, et al. Wavelets and functional magnetic resonance imaging of the human brain. Neuroimage 2004;23 Suppl 1:S234-49.

Bullmore E, Sporns O. The economy of brain network organization. Nat.Rev.Neurosci. 2012;13:336-349.

Chialvo DR. Emergent complex neural dynamics. Nature Physics 2010;6:744-750.

Egner T, Zech TF, Gruzelier JH. The effects of neurofeedback training on the spectral topography of the electroencephalogram. Clin.Neurophysiol. 2004;115:2452-2460.

Escolano C, Aguilar M, Minguez J. EEG-based upper alpha neurofeedback training improves working memory performance. Conf.Proc.IEEE Eng.Med.Biol.Soc. 2011;2011:2327-2330.

Gilden DL, Thornton T, Mallon MW. 1/f Noise in Human Cognition. Science 1995;267:1837-1839.

Gruzelier JH. EEG-neurofeedback for optimising performance. I: a review of cognitive and affective outcome in healthy participants. Neurosci.Biobehav.Rev. 2014a;44:124-141.

Gruzelier JH. EEG-neurofeedback for optimising performance. III: a review of methodological and theoretical considerations. Neurosci.Biobehav.Rev. 2014b;44:159-182.

Hardstone R, Poil SS, Schiavone G, Jansen R, Nikulin VV, Mansvelder HD, et al. Detrended fluctuation analysis: a scale-free view on neuronal oscillations. Front.Physiol. 2012;3:450.

He BJ. Spontaneous and task-evoked brain activity negatively interact. J.Neurosci. 2013;33:4672-4682.

ACCEPTED MANUSCRIPT

Jensen O, Bahramisharif A, Oostenveld R, Klanke S, Hadjipapas A, Okazaki YO, et al. Using brain-computer interfaces and brain-state dependent stimulation as tools in cognitive neuroscience. Front.Psychol. 2011;2:100.

Kamiya J. Conscious control of brain waves. Psychology Today 1968;1:57-4.

Kaplan A, Shishkin S, Ganin I, Basyul I, Zhigalov A. Adapting the P300-Based Brain–Computer Interface for Gaming: A Review. Computational Intelligence and AI in Games, IEEE Transactions on 2013;5:141-149.

Kaplan AY, Lim JJ, Jin KS, Park BW, Byeon JG, Tarasova SU. Unconscious operant conditioning in the paradigm of brain-computer interface based on color perception. Int J Neurosci. 2005;115:781-802.

Kinouchi O, Copelli M. Optimal dynamical range of excitable networks at criticality. Nature Physics 2006;2:348-351.

Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res.Brain Res.Rev. 1999;29:169-195.

Kruglikov SY, Schiff SJ. Interplay of electroencephalogram phase and auditory-evoked neural activity. J.Neurosci. 2003;23:10122-10127.

Kumano H, Horie H, Shidara T, Kuboki T, Suematsu H, Yasushi M. Treatment of a depressive disorder patient with EEG-driven photic stimulation. Biofeedback Self Regul. 1996;21:323-334.

Linden DE. Neurofeedback and networks of depression. Dialogues Clin.Neurosci. 2014;16:103-112.

Linkenkaer-Hansen K, Monto S, Rytsala H, Suominen K, Isometsa E, Kahkonen S. Breakdown of long-range temporal correlations in theta oscillations in patients with major depressive disorder. J.Neurosci. 2005;25:10131-10137.

Linkenkaer-Hansen K, Nikouline VV, Palva JM, Ilmoniemi RJ. Long-range temporal correlations and scaling behavior in human brain oscillations. J.Neurosci. 2001;21:1370-1377.

Linkenkaer-Hansen K, Nikulin VV, Palva JM, Kaila K, Ilmoniemi RJ. Stimulus-induced change in long-range temporal correlations and scaling behaviour of sensorimotor oscillations. Eur.J.Neurosci. 2004;19:203-211.

Massimini M, Boly M, Casali A, Rosanova M, Tononi G. A perturbational approach for evaluating the brain's capacity for consciousness. Prog.Brain Res. 2009;177:201-214.

Mathewson KE, Prudhomme C, Fabiani M, Beck DM, Lleras A, Gratton G. Making waves in the stream of consciousness: entraining oscillations in EEG alpha and fluctuations in visual awareness with rhythmic visual stimulation. J.Cogn.Neurosci. 2012;24:2321-2333.

Montez T, Poil SS, Jones BF, Manshanden I, Verbunt JP, van Dijk BW, et al. Altered temporal correlations in parietal alpha and prefrontal theta oscillations in early-stage Alzheimer disease. Proc.Natl.Acad.Sci.U.S.A. 2009;106:1614-1619.

Monto S, Vanhatalo S, Holmes MD, Palva JM. Epileptogenic Neocortical Networks Are Revealed by Abnormal Temporal Dynamics in Seizure-Free Subdural EEG. Cerebral Cortex 2007;17:1386-1393.

ACCEPTED MANUSCRIPT

Ngo HV, Martinetz T, Born J, Molle M. Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron 2013;78:545-553.

Nikulin VV, Jonsson EG, Brismar T. Attenuation of long-range temporal correlations in the amplitude dynamics of alpha and beta neuronal oscillations in patients with schizophrenia. Neuroimage 2012;61:162-169.

Palva JM, Zhigalov A, Hirvonen J, Korhonen O, Linkenkaer-Hansen K, Palva S. Neuronal long-range temporal correlations and avalanche dynamics are correlated with behavioral scaling laws. Proc.Natl.Acad.Sci.U.S.A. 2013;110:3585-3590.

Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. Chaos 1995;5:82-87.

Poil SS, Hardstone R, Mansvelder HD, Linkenkaer-Hansen K. Critical-State Dynamics of Avalanches and Oscillations Jointly Emerge from Balanced Excitation/Inhibition in Neuronal Networks. J.Neurosci. 2012;32:9817-9823.

Prichard D, Theiler J. Generating surrogate data for time series with several simultaneously measured variables. Phys.Rev.Lett. 1994;73:951-954.

Romei V, Thut G, Mok RM, Schyns PG, Driver J. Causal implication by rhythmic transcranial magnetic stimulation of alpha frequency in feature-based local vs. global attention. Eur.J.Neurosci. 2012;35:968-974.

Ros T, J Baars B, Lanius RA, Vuilleumier P. Tuning pathological brain oscillations with neurofeedback: a systems neuroscience framework. Front.Hum.Neurosci. 2014;8:1008.

Ros T, Munneke MA, Ruge D, Gruzelier JH, Rothwell JC. Endogenous control of waking brain rhythms induces neuroplasticity in humans. Eur.J.Neurosci. 2010;31:770-778.

Scharnowski F, Hutton C, Josephs O, Weiskopf N, Rees G. Improving visual perception through neurofeedback. J.Neurosci. 2012;32:17830-17841.

Scheeringa R, Mazaheri A, Bojak I, Norris DG, Kleinschmidt A. Modulation of visually evoked cortical FMRI responses by phase of ongoing occipital alpha oscillations. J.Neurosci. 2011;31:3813-3820.

Shew WL, Plenz D. The functional benefits of criticality in the cortex. Neuroscientist 2013;19:88-100.

Shew WL, Yang H, Petermann T, Roy R, Plenz D. Neuronal avalanches imply maximum dynamic range in cortical networks at criticality. J.Neurosci. 2009;29:15595-15600.

Shew WL, Yang H, Yu S, Roy R, Plenz D. Information capacity and transmission are maximized in balanced cortical networks with neuronal avalanches. J.Neurosci. 2011;31:55-63.

Smit DJ, Linkenkaer-Hansen K, de Geus EJ. Long-range temporal correlations in resting-state alpha oscillations predict human timing-error dynamics. J.Neurosci. 2013;33:11212-11220.

Strehl U, Birkle SM, Worz S, Kotchoubey B. Sustained reduction of seizures in patients with intractable epilepsy after self-regulation training of slow cortical potentials - 10 years after. Front.Hum.Neurosci. 2014;8:604.

ACCEPTED MANUSCRIPT

Studer P, Kratz O, Gevensleben H, Rothenberger A, Moll GH, Hautzinger M, et al. Slow cortical potential and theta/beta neurofeedback training in adults: effects on attentional processes and motor system excitability. Front.Hum.Neurosci. 2014;8:555.

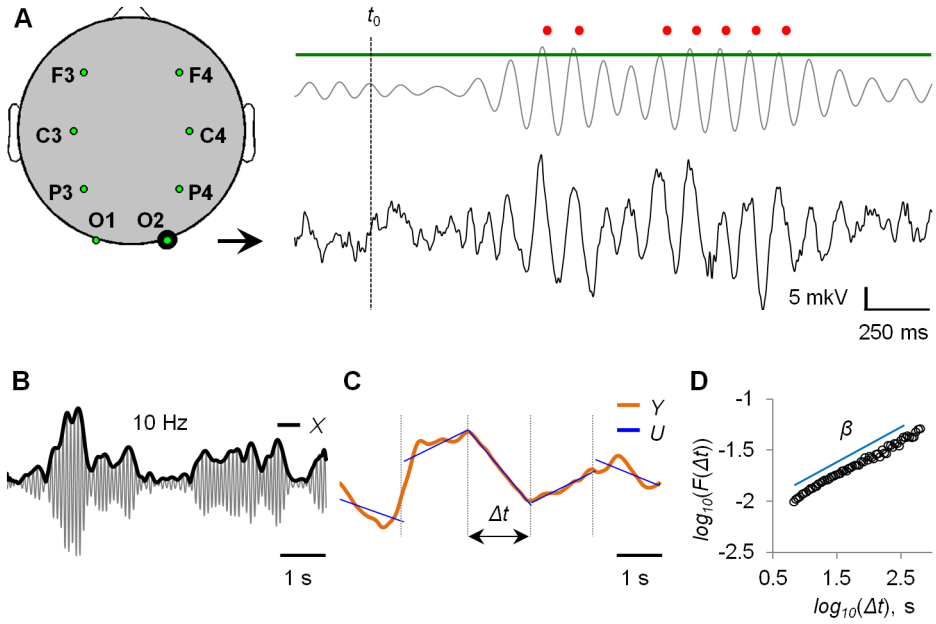
Wang XJ. Neurophysiological and computational principles of cortical rhythms in cognition. Physiol.Rev. 2010;90:1195-1268.

Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. Clin.Neurophysiol. 2002;113:767-791.

Zhigalov A, Arnulfo G, Nobili L, Palva S, Palva JM. Relationship of Fast- and Slow-Timescale Neuronal Dynamics in Human MEG and SEEG. J.Neurosci. 2015;35:5385-5396.

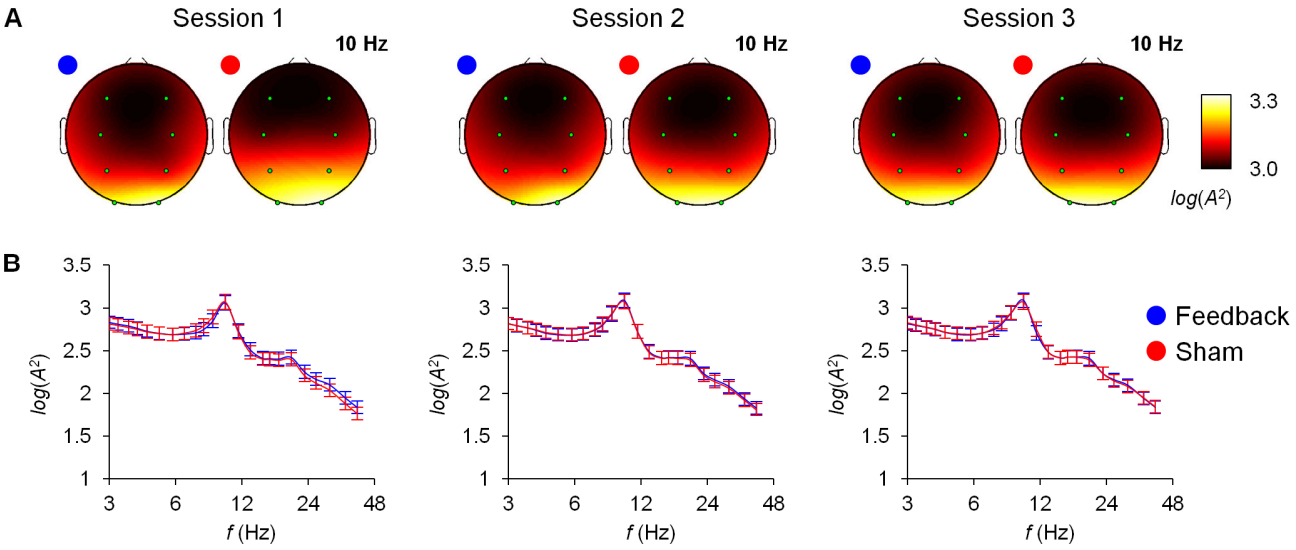
Zoefel B, Huster RJ, Herrmann CS. Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. Neuroimage 2011;54:1427-1431.

ACCEPTED MANUSCRIPT

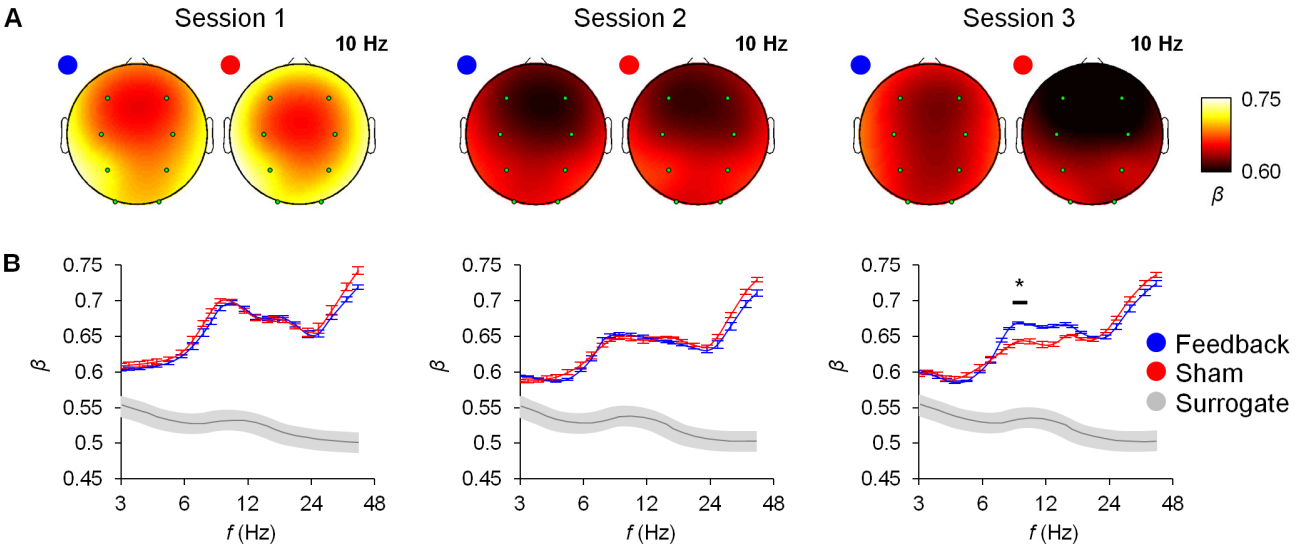


ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

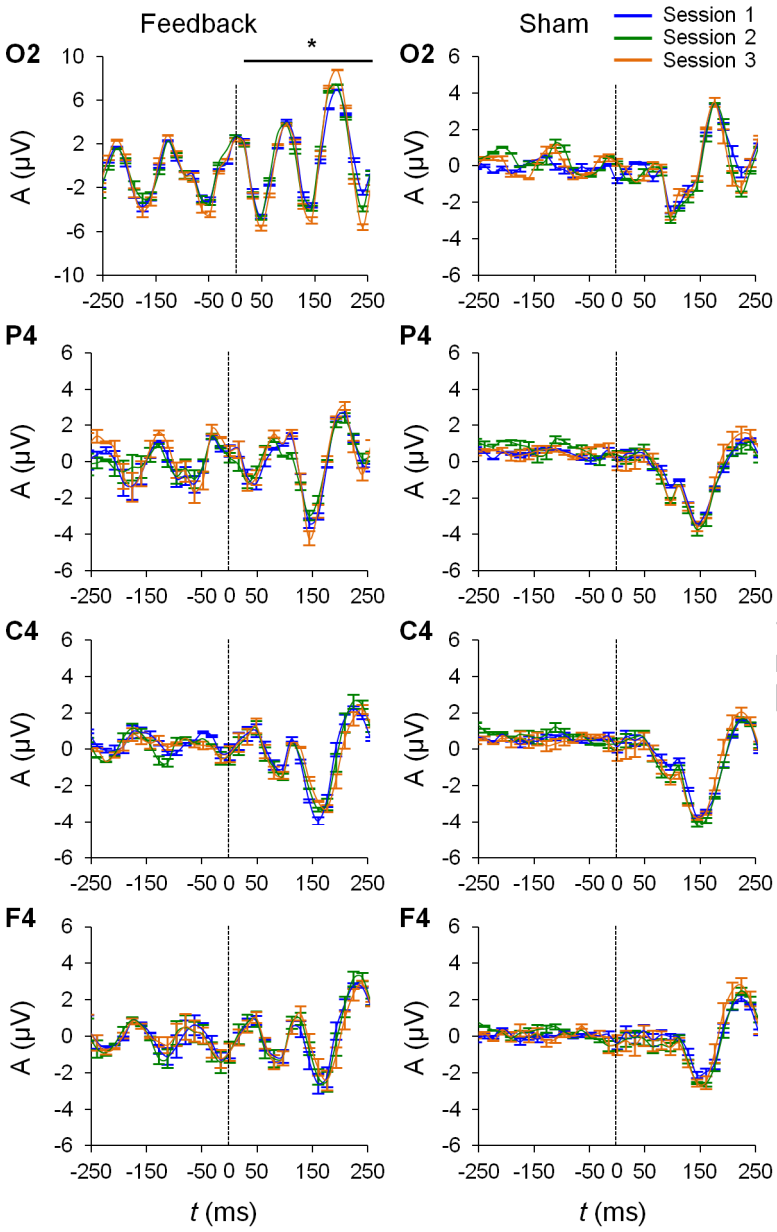


ACCEPTED MANUSCRIPT



ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT



ACCEPTED MANUSCRIPT