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Modulation of critical brain dynamics using closed-loop neurofeedback stimulation

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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 progressively enhanced 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.
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.

1. Introduction

Several lines of electrophysiological (Linkenkaer-Hansen et al., 2001), blood-oxygenation-level dependent (BOLD) signal imaging

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(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 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, 2014; Studer 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.

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; 3 mm, 2.5 cd) mounted on