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Does Transcranial Alternating Current Stimulation Induce Cerebellum Plasticity? Feasibility, Safety and Efficacy of a Novel Electrophysiological Approach

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ABSTRACT

Background: Cerebellum-brain functional connectivity can be shaped through different non-invasive neurostimulation approaches. In this study, we propose a novel approach to perturb the cerebellum-brain functional connectivity by means of transcranial alternating current stimulation (tACS).
Methods: Twenty-five healthy individuals underwent a cerebellar tACS protocol employing different frequencies (10, 50, and 300 Hz) and a sham-tACS over the right cerebellar hemisphere. We measured their after-effects on the motor evoked potential (MEP) amplitude, the cerebellum-brain inhibition (CBI), the long-latency intracortical inhibition (LICI), from the primary motor cortex of both the hemispheres. In addition, we assessed the functional adaptation to a right hand sequential tapping motor task.
Results: None of the participants had any side-effect. Following 50 Hz-tACS, we observed a clear contralateral CBI weakening, paralleled by a MEP increase with a better adaptation to frequency variations during the sequential tapping. The 300 Hz-tACS induced a contralateral CBI strengthening, without significant MEP and kinematic after-effects. The 10 Hz-tACS conditioning was instead ineffective.
Conclusions: We may argue that tACS protocols could have interfered with the activity of CBI-sustaining Purkinje cell, affecting motor adaptation. Our safe approach seems promising in studying the cerebellum-brain functional connectivity, with possible implications in neurorehabilitative settings.
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Introduction

The cerebellum is involved in several motor and cognitive functions, including maintenance of balance and posture, coordination of voluntary movements, and motor learning [1]. It has been shown that cerebral sensory processing, as well as the primary motor cortex excitability (M1) [2–4], can be shaped by means of non-invasive neurostimulation protocols over the cerebellum, including the transcranial direct current stimulation (tDCS) and the transcranial magnetic stimulation (TMS). Such approaches may affect some aspects of the cerebellum-M1 connectivity [5–8], which can be assessed by means of cerebellum-brain inhibition (CBI) paradigm [6,9–11], consisting in the inhibitory effect of conditioning magnetic stimulus delivered over cerebellar hemisphere on motor evoked potential (MEP) amplitude in the contralateral M1.

Nonetheless, the physiology of cerebellar-M1 connectivity and cerebellar excitability is complex, due to the composite cerebellar cortex connectivity and the wide and overlapping frequency spectra of cerebellar oscillations (up to approximately 300 Hz) [12–15]. Within cerebellar elements, Purkinje cells (PC) are tonically active but they also show high-frequency bursts following incoming stimuli or efferent motor actions [16]. Therefore, the modulation of this firing rate could result in either an increase or a decrease of oscillatory activity in several frequency bands, depending on a variety of factors, including the level of synchrony across local populations.

Recently, a particular type of non-invasive transcranial electric stimulation employing sinusoidal currents, namely transcranial alternating current stimulation (tACS), has been applied in shaping cortical oscillations. The advantage offered by tACS consists in the possibility to perturb brain oscillatory activity by either sinusoidally modulating the membrane voltage or entraining the oscillations (by means of phase-shifting or power-modulation) [17]. This could allow researchers to specifically modulate some cerebellar activity, in analogy to tACS application on cerebral cortex. In this work

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we applied a tACS conditioning protocol at different frequencies over the right cerebellar hemisphere, in an attempt to modulate the contralateral M1 excitability and CBI, evaluating the safety, the feasibility, and the efficacy of such method. We adopted three main stimulation frequency that have been reported to be involved in the synchronization among granule cells and parallel fibers (~10 Hz), basal firing frequency of PC (~50 Hz), and feedback firing pattern of Golgi cells (~300 Hz) [11,12,18–28]. Moreover, we evaluated the adaptation rate to external perturbations during a hand sensory-motor synchronization task (SMS), since cerebellum seems to have an important role in such adaptive motor learning [2,3].

Methods

Subjects

We enrolled in this study 25 healthy right-handed volunteers (14 female and 11 male; mean age 37 ± 6 years). None of the subjects had a history of neurologic and/or psychiatric disorders. All of the participants were naïve for the aim of the study. The written informed consent was obtained from each enrolled individual.

Experimental design

Each subject performed a standard electroencephalographic (EEG) assessment. Thus, we applied a cerebellar 50 Hz-tACS conditioning protocol, immediately followed by EEG recording, in order to assess eventual electric activity modifications.

After one week from the preliminary EEG recording, the enrolled participants underwent the experimental procedure. Subjects were sitting on a comfortable reclining chair while performing the experiment. At baseline (T_{PRE}), we measured some electrophysiological parameters by means of TMS, and the motor adaptation performance through a SMS task. Thus, we applied a tACS conditioning protocol at 10, 50, and 300 Hz, and a sham-tACS. We repeated the same baseline measures immediately (T_0), 15 (T_{15}), and 30 min (T_{30}) after the end of the conditioning protocol. A 3 min EEG was also recorded at T_0. Each subject practiced all of the conditioning protocols, in a random order of stimulation and with a one-week interval. The participants and the experimenters who analyzed the data were blinded on the stimulation order. The experimental procedure is summarized in Fig. 1.

Transcranial magnetic stimulation

We registered 15 MEPs, 10 CBI, and 10 long-latency intracortical inhibition (LICI), randomly intermingled in single trials, at a frequency of 0.2 Hz, from both hemispheres, at T_{PRE}, T_0, T_{15}, and T_{30}.

MEPs were obtained through magnetic monophasic stimuli delivered through a high-power Magstim200 Stimulator (Magstim, Whitland, Dyfed, UK). The rise time of the magnetic monophasic stimulus was about 100 µs with a to-zero of about 800 µs. The current flowed in handle direction during the rise-time of the magnetic field. At first, the coil was placed tangentially to the scalp with the handle pointing backwards and laterally, at a 45° angle to the sagittal plane, approximately perpendicular to the central sulcus of

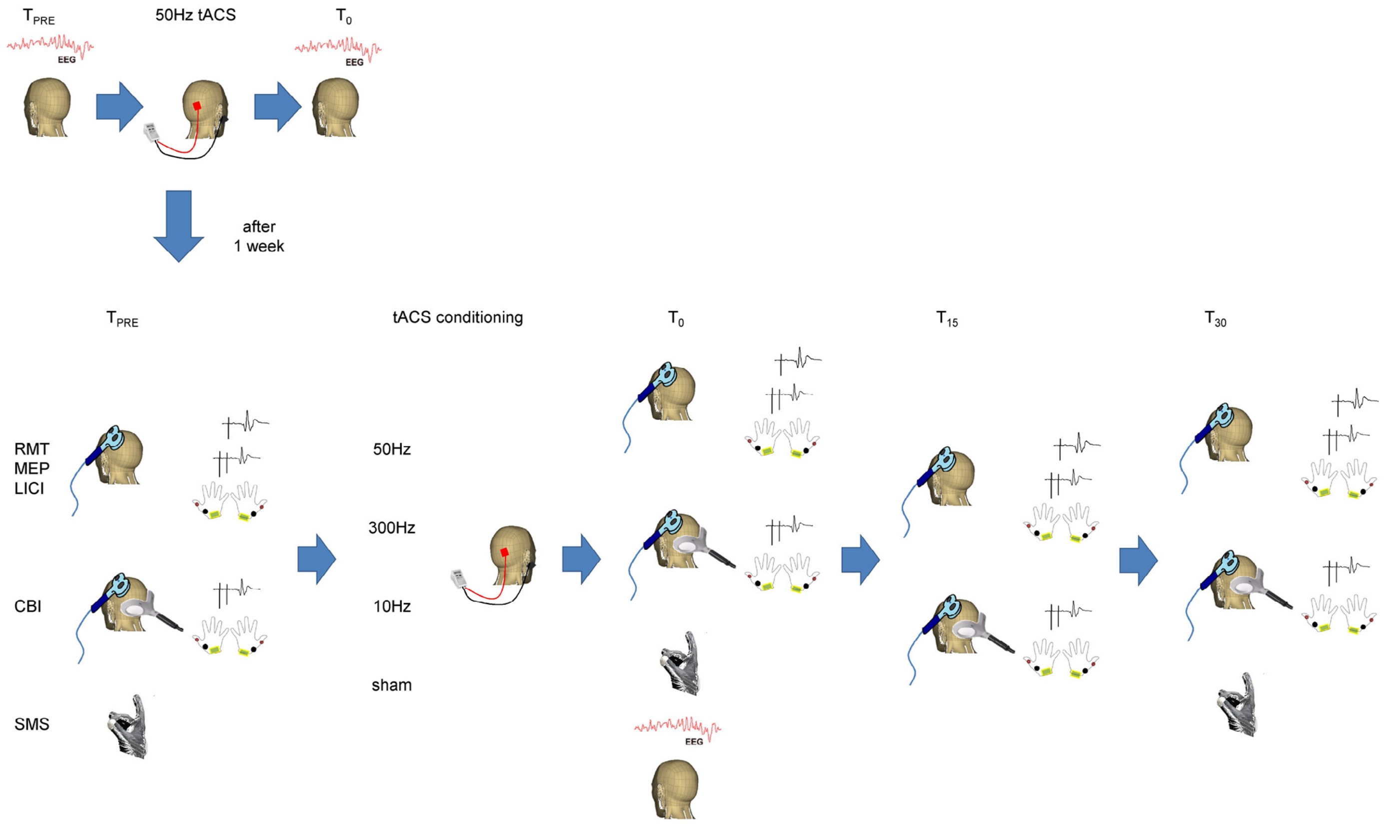

Figure 1. Summarizes the experimental procedure. Preliminarily, each subject performed a standard electroencephalographic (EEG) assessment, which was also recorded immediately after a cerebellar 50 Hz-tACS conditioning protocol. After one week, we measured the resting motor threshold (RMT), the motor evoked potential (MEP) amplitude, the long-latency intracortical inhibition (LICI), the cerebellum-brain inhibition (CBI), and the motor adaptation at a sensory-motor synchronization (SMS) task at baseline (T_{PRE}). Then, we applied a tACS conditioning protocol at 10, 50, and 300 Hz, and a sham-tACS, with a random order of stimulation and with a one-week interval. Thus, we repeated the same baseline measures immediately (T_0), 15 (T_{15}), and 30 min (T_{30}) after the end of the conditioning protocol. The kinematic assessment was performed only at T_0 and T_{30}. An EEG was recorded at T_0.

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