PERSPECTIVES

Rippling the cortex with high-frequency (>100 Hz) alternating current stimulation

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A wide range of non-invasive brain stimulation techniques are currently available which can induce lasting changes in the excitability of the stimulated cortex (Ziemann *et al.* 2008). Regular repetitive transcranial magnetic stimulation (rTMS) and constant transcranial direct current stimulation (c-tDCS) are well-established stimulation modalities that have now been used for more than 10 years. Other stimulation techniques have only recently been introduced, such as continuous transcranial alternating current stimulation (c-tACS), oscillatory tDCS (o-tDCS) or patterned rTMS protocols.

Currently, c-tDCS uses weak currents up to 2 mA which induce currents in the cortex that are far below the threshold for inducing action potentials. The tissue current is still strong enough to polarise the membrane potential of cortical neurons, resulting in lasting shifts in the resting membrane potential and associated changes in post-synaptic spiking activity. These effects are thought to mediate the after-effects of c-tDCS. A different mechanism is emphasized when c-tACS is used to manipulate cortical plasticity. Here the assumption is that the oscillatory current interacts with and shapes intrinsic neural oscillations in the stimulated cortex. Indeed recent studies support this notion showing that c-tACS can interact with brain function in a frequency specific manner (Kanai *et al.* 2008; Pogosyan *et al.* 2009).

In an article in this issue of *The Journal of Physiology*, Moliadze *et al.* (2010) significantly add to this line of research. In healthy volunteers, 10 min of c-tACS of the human motor hand area ($M1_{hand}$) at 140 Hz but not at 80 Hz enhanced regional corticospinal excitability during and for at least an hour after c-tACS. At 250 Hz, c-tACS also induced an increase in corticospinal excitability but to a lesser extent and with a delayed onset of facilitation. The increase in corticospinal excitability (measured by motor evoked potential amplitude in a hand muscle) was paralleled by a relative decrease in short latency intracortical inhibition (SICI), an electrophysiological marker of $GABA_A$ receptor mediated inhibition.

Although Moliadze *et al.* (2010) are cautious to draw firm conclusions, they favour the hypothesis that tACS at 140 Hz targets cortical ripples and the resulting after-effects are due to an interaction between externally applied high frequency oscillation in the ripple range and intrinsic cortical ripple activity in $M1_{hand}$. This is a possible scenario as ripple oscillations in the frequency range from 80 to 200 Hz have been demonstrated in the cat cortex, yet they are mainly expressed during non-REM sleep (Grenier *et al.* 2001). Furthermore, pulsed stimulation in the ripple range (130 Hz) of afferents to the subthalamic nucleus is therapeutically effective in Parkinsonian rodents (Gradinaru *et al.* 2009) and is being used for deep brain stimulation in human patients.

The perspective that transcranial stimulation can be tuned to specifically target cortical oscillatory in specific frequency bands is intriguing. Oscillatory patterning of neuronal activity in different frequency bands supports temporal coding of different aspects of cortical processing (Singer, 2009). Therefore, transcranial stimulation protocols that can efficiently manipulate specific oscillatory activity might be more efficient and specific with respect to shaping specific brain functions than conventional regular rTMS or c-tDCS. At first glance, it seems straightforward to postulate that transcranial stimulation protocols should mimic as close as possible the temporal pattern of the intrinsic cortical oscillations that one wishes to modulate with transcranial stimulation. However, a number of general questions need to be clarified.

Which stimulus intensity is most effective in shaping cortical oscillations?

As mentioned above, c-tDCS and c-tACS use very low intensities of stimulation which modulate the neuronal potential without directly evoking spiking activity. If low-intensity stimulation is most efficient to modulate oscillatory brain activity, high-frequency rTMS at very low intensities (e.g. at intensities below 10% of resting motor threshold) might be as effective as c-tDCS or c-tACS but more focal.

Another consideration is that high-intensity transcranial stimulation protocols might be preferable if one intends to enhance the expression of the dominant oscillatory activity in a given cortical region. Combination of single-pulse TMS with high-density electroencephalography (EEG) showed that a single TMS pulse consistently evoked dominant alpha-band oscillations (8–12 Hz) in the occipital cortex, beta-band oscillations (13–20 Hz) in the parietal cortex, and fast gamma-band oscillations (21–50 Hz) in the frontal cortex (Rosanova *et al.* 2009). Therefore, an efficient stimulation strategy might be to apply a rTMS protocol at conventional intensities but very low frequency and thereby repeatedly induce the expression of the local cortical rhythm.

Is a continuous mode of stimulation more efficient in boosting cortical oscillations as opposed to a pulsed or patterned mode of stimulation?

All cortical oscillations show strong spontaneous modulations over time, in term of both their expression and their amplitude. For instance, ripple activity is expressed intermittently in the cortex and therefore it is questionable whether continuous stimulation at ripple frequency is the most efficient way to entrain and boost intrinsic ripple activity. More complex patterns of temporal stimulation such as intermittent periods of stimulation might be preferable. Ideally, one might use on-line EEG recordings to trigger the external induction of oscillatory activity and thereby cause a temporal alignment of intrinsic and

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extrinsically induced oscillations. Such an approach would also account for the context dependency of the regional expression of cortical oscillations.

Is it necessary that the transcranial stimulation protocol reflects the temporal features of the cortical oscillation?

Before subscribing to a stimulation strategy that tries to imitate the cortical rhythm, one also needs to study the lasting effects of stimulation protocols that 'ignore' the oscillatory features on intrinsic cortical oscillations. The critical question is what can be gained by applying oscillatory compared to non-oscillatory protocols. Of note, random noise tACS of the $M1_{hand}$ at a frequency range from 100 to 640 Hz (Terney *et al.* 2008) elicited comparable changes in corticospinal excitability as compared to oscillatory tACS at 140 Hz (Moliadze *et al.* 2010). Likewise, slow-oscillatory tDCS at 0.8 Hz of the $M1_{hand}$ had comparable acute and lasting effects on corticospinal excitability to c-tDCS when the total amount of applied current was matched (Groppa *et al.* 2010). Despite these acute and lasting effects, no phase-locking of corticospinal excitability to the exogenous oscillation was observed during slow-oscillatory tDCS (Bergmann *et al.* 2009).

These considerations raise the question whether choosing an oscillatory mode of low-intensity brain stimulation guarantees a more efficient modulation of intrinsic cortical oscillations or stronger changes in regional cortical excitability than non-oscillatory modes of stimulation. To tackle this important question, more studies are needed that combine interventional cortex stimulation with concurrent EEG measurements in humans. These studies should be paralleled by animal studies in which the impact of oscillatory *versus* non-oscillatory cortex stimulation on cortical oscillatory activity is directly assessed using invasive recordings. This will provide a more sophisticated neurobiological framework in which future brain stimulation protocols can be tailored to the intrinsic susceptibility of the stimulated cortical area.

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