



## Editorial

## Tuning out the Blues – Thalamo-Cortical Rhythms as a Successful Target for Treating Depression



Today's most prevalent neuromodulation approaches such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) were designed to modulate neuronal activity levels. Yet, overall activity levels by themselves reflect only one aspect of neuronal coding and information processing. In particular, both physiological and pathological behavioral states map onto temporally-patterned electric activity in large-scale neuronal networks [1,2]. In the case of psychiatric disorders, specific changes in the rhythmic activity structure of (thalamo-) cortical networks have been identified that correlate with behavioral and cognitive symptoms [3]. These pathological network dynamics represent a promising target for brain stimulation [4,5].

In a ground-breaking study, Leuchter and colleagues ([6], prior issue) performed a multi-center, double-blind, sham-controlled, randomized clinical trial to evaluate the clinical efficacy of synchronized transcranial magnetic stimulation (sTMS). sTMS is a novel type of non-invasive brain stimulation that was explicitly designed to target network dynamics for the treatment of major depressive disorder (MDD). Specifically, sTMS aims to renormalize alpha oscillations that are altered in individuals with depression [7]. sTMS employs spinning static magnets to provide a weak electromagnetic field that is temporally patterned to match the individual peak frequency in the EEG alpha frequency band. Therefore, sTMS is an individualized treatment that combines probing of brain dynamics with EEG to establish the individual alpha frequency (IAF) together with stimulation at the IAF. The clinical results in this trial look very encouraging and clearly deserve close attention by the field.

Fundamentally, sTMS rests on two key assumptions. The first assumption is that frequency-matched stimulation resets pathological alpha oscillations. The second assumption is that such resetting leads to a clinical benefit for patients with MDD. The current study demonstrates a clinical effect of sTMS, but only follow-up analyses

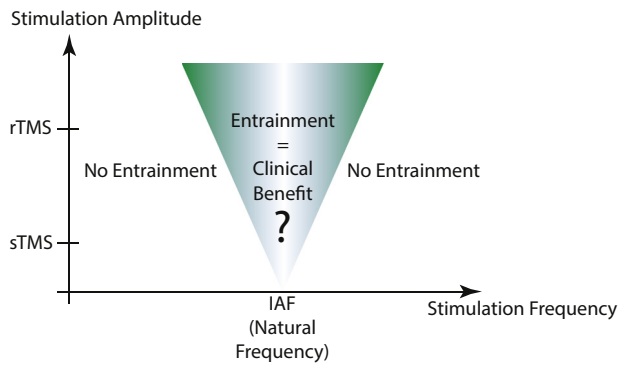
of the electrophysiological data and new studies will elucidate the effect of sTMS on network dynamics (in support of the first assumption). In the Leuchter trial, the researchers attempted to match the stimulation to the IAF of the patient. For some patients, the analysis program did not work and they were stimulated at a frequency different from their IAF. As a group, they did not have a beneficial clinical outcome. The field needs a formal study testing this key concept, where some patients are stimulated at IAF and others on purpose are stimulated at a frequency different from IAF. That would help test whether frequency matching is indeed critical to the effects.

How can a weak electromagnetic field alter brain function and behavior? Dynamic systems theory predicts that an endogenous oscillator can be entrained by an external periodic force that needs to satisfy specific requirements referred to as the Arnold tongue (Fig. 1). In essence, periodic stimulation can phase-lock (or synchronize) the targeted oscillator as long as the stimulation frequency is sufficiently close to the endogenous (i.e. natural) oscillation frequency. The higher the stimulation amplitude, the broader the range of frequencies around the natural frequency at which the perturbation can entrain the oscillator. Can the complexity of the interaction between neuronal networks and non-invasive stimulation be reduced to this theoretical model? Indeed, the presence of an Arnold tongue has been previously demonstrated in large-scale computer simulations of cortical networks that were subject to a weak sine-wave stimulation waveform [8]. Experimentally, similar effects of frequency preference have been demonstrated in acute neocortical [9,10] and hippocampal [11] brain slices. Intriguingly, Leuchter and colleagues present data that agree with this model – notably in terms of clinical efficacy – since matching the stimulation frequency to IAF was essential for achieving a therapeutic benefit in individual patients. Likely, the net change in membrane voltage induced by sTMS is relatively small and corresponds to the tip of the Arnold tongue where frequency-matching (to limit detuning) between endogenous and stimulation frequencies is vital to achieve synchronization (and thereby therapeutic benefits).

For understanding the network-level mechanism(s) of sTMS, the similarities of sTMS with transcranial alternating current stimulation (tACS), another non-invasive brain stimulation modality that targets cortical oscillations [12], are instructive. TACS applies a low-amplitude, sine-wave electric current to the scalp that results in a weak, periodic electric field in the brain. The resulting change in somatic membrane voltage by tACS is likely less than a millivolt.

Conflict of interest: UNC has filed several patents on tACS-related technology and applications with Flavio Frohlich as the lead inventor. No licensing has occurred and none of the authors are financially or otherwise benefitting from this initial filing. Flavio Frohlich has received travel funding from Tal Medical and is slated to act as a CO-PI for a Neosync study site and receive research support from Tal Medical. Flavio Frohlich is the PI on several clinical trials that study tACS in psychiatric applications, including major depressive disorder.

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**Figure 1.** Cartoon representation of the Arnold tongue in the context of non-invasive brain stimulation. The shaded triangular area (“tongue-shaped”) represents the combination of stimulation frequencies and amplitudes that successfully entrain endogenous oscillations, here alpha oscillations. The stimulation amplitude of sTMS may be low enough to require close matching of the stimulation frequency to the natural (endogenous) frequency (IAF) for entrainment and therefore a clinical benefit. In contrast, the same frequency tuning may not be needed for rTMS due to the higher stimulation amplitude (under the assumption that the therapeutic benefit relates to entraining alpha oscillations).

In contrast to transcranial magnetic stimulation, tACS (and by extension) sTMS does not provide a super-threshold perturbation that triggers action potentials. Rather, the change in membrane voltage introduced by stimulation interacts with the endogenous network dynamics. Computer simulations and slice experiments propose that the mechanism of action is based on the above discussed Arnold tongue concept of synchronization. Synchronization is achieved by modulating the spike-timing of neurons at threshold; due to the strong non-linearity at the threshold for action potential initiation, even a very small perturbation can alter the timing of individual action potentials [13]. If applied to a large network (due to the lack of spatial focality of tACS, and likely sTMS), large-scale networks are synchronized by such modulation of spike-timing since synaptic interactions amplify and propagate the effect of the perturbation.

It is important to emphasize that the research on understanding the neurobiological effects of tACS and sTMS is still in its infancy. Several basic questions remain unanswered. For example, despite the use of tACS at IAF [14], no converging evidence has so far been presented that demonstrates the necessity of such individual tuning of the stimulation frequency [15]. Furthermore, the effect of tACS in the alpha frequency band appears to be state-dependent [16]; an enhancement of alpha oscillations was only found for the eyes-open awake state and not for the eyes-closed awake state (as used by Leuchter and colleagues). At the mechanistic level, it is unclear how stimulation that likely enhances alpha oscillations (based on the tACS literature) can renormalize the pathological increase of alpha oscillations found in the left hemisphere of patients with MDD [17]. Also, it is unclear how repeated treatment sessions provide a cumulative benefit; likely, the mechanism goes beyond just instantaneous entrainment during stimulation. For example, in the case of tACS, an argument for neuroplasticity causing outlasting effects has been recently made [18].

At this point, it appears fair to say that there are a number of unresolved questions about the mechanism of action of sTMS (and other non-invasive stimulation modalities that target alpha oscillations). Nevertheless, there is a very strong rationale for targeting alpha oscillations. Further support for this approach derives from the fact that FDA-approved rTMS [19] employs a 10 Hz waveform that has recently been demonstrated to entrain alpha oscillations [20]. It is not uncommon for a new treatment to be discovered before the underlying mechanism has been fully elucidated. Computer simulations and work in preclinical animal models will help

to fill this gap. Once we understand the mechanisms of sTMS, it is conceivable that through rational design the clinical efficacy can be even further improved.

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