Methods: Ultrasonic neuromodulation has been demonstrated in rodents, non-human primates and healthy volunteers. We will first review the pioneering studies on transcranial ultrasonic neuromodulation. Transient effects (lasting less than 1s) were initially induced. The acoustical stimulation parameters were further optimized to extend the duration of the neuromodulation to more than an hour (Verhagen et al. 2019), in line with potential clinical applications. Nevertheless, the first proofs of concept on healthy volunteers were limited to cortical stimulations because of the defocusing effect of the human skull. To counteract this, transcranial focusing was initially achieved by using multi-element arrays made of hundreds of ultrasound transducers. But a disruptive approach was introduced recently: it consists in the use of a single-element transducer covered with a 3D printed acoustic lens (Maimbourg et al. 2018) (Figure 1). The acoustic lens also enables non-invasive simultaneous multisite deep brain stimulation.

Conclusions: Altogether, the demonstration of sustained ultrasonic neuromodulation and the development of precise, low cost and mobile prototypes for noninvasive deep brain ultrasound focusing indicate that Transcranial Ultrasound Stimulation is now ready for clinical translation.

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COMBINING APP-BASED PSYCHOLOGICAL INTERVENTION WITH HOME-BASED TRANSCRANIAL DIRECT STIMULATION FOR THE TREATMENT OF DEPRESSIVE AND ANXIETY SYMPTOMS: A CASE SERIES

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Evidence indicates high heterogeneity in tDCS efficacy as a stand-alone treatment. Combining tDCS with psychological interventions may yield promising results to increase its therapeutic effects (Dedoncker et al. 2021). The current case series details the effects of 6 weeks of self-administered tDCS paired with behavioral therapy smartphone app (using Flow™), on depressive and anxiety symptoms, in seven patients (26-51y; 5 female) presenting distinctive neuropsychiatric disorders. The stimulation protocols consisted of 30min daily sessions, for 10 working days (two weeks from Monday-to-Friday; Protocol 1) or 15 consecutive workdays (three weeks from Monday-to-Friday; Protocol 2), followed by twice-weekly sessions for 2 or 3 weeks, respectively (18 or 21 sessions in total). Flow™ uses a current intensity of 2mA, targeting the bilateral dorsolateral prefrontal cortex. The app offers virtually guided sessions of behavioral therapy to be completed during stimulation which are not mandatory. At baseline and week 6 of treatment, we assessed depressive symptoms using MADRS-s and BDI-II, anxious symptoms using STAI-Trait, acceptability using ACCEPT-ETCC, and side effects using the Portuguese translation of the Thair et al. questionnaire (Thair et al. 2017). According to the Reliable Change Index (RCI), clinically reliable changes were found in symptoms of depression in 4 patients using MADRS-s (out of 7; RCI: -1.44 to -4.82; 90% CI) and in 3 patients using BDI-II (out of 4; RCI: -3.61 to -6.18; 90% CI). For anxiety symptoms, we found clinically reliable improvement in 4 patients (out of 5; RCI: -1.79 to -8.64; 90% CI). Stimulation was well tolerated and accepted (M=87.71, SD=4.92), with mild tingling sensation and scalp discomfort being the most common side effects. This case series highlights the applicability, acceptance, and promising results of combined home-based tDCS and app-based psychological interventions for the treatment of depression and anxiety symptoms.

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MODELLING NON-INVASIVE BRAIN STIMULATION OF DEEP BRAIN STRUCTURES FOR PSYCHIATRIC APPLICATIONS

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Introduction: Recent neuropathological and neuroimaging work has identified the lateral habenula as a critical deep brain structure that likely contributes to the neuro-pathophysiology of prevalent psychiatric illnesses. The ability to modulate deep psychiatric targets will become critical to the development of novel treatment protocols and modalities. This is a computational modelling study to explore two common (transcranial alternating current stimulation (tACS) and transcranial magnetic stimulation (TMS)) and one novel (temporally interfering electric fields (TI EFs)) non-invasive brain stimulation (NIBS) methods in their ability to reach and modulate deep brain targets, and anticipate relevant local effects.

Methods: Firstly, the relative strengths of electric fields on- and off-target, a novel target of the lateral habenula in humans, are modelled and compared using simulations based on human neuroimaging data with SimNIBS. Secondly, local effects of these field strengths are modelled on single-compartment neuronal models. Finally, potential side effects such as conduction blocks are investigated using simple single-compartment neuronal models to assess the diverse potential impact of field strength on neuronal activity on- and off-target in the brain.

Results: Across the studied NIBS modalities, the ratio of maximum electric field strength off-target to that at the target remains high, especially for figure-8 coil TMS. Investigation of local effects suggests that the field strengths of all the studied NIBS modalities engage off-target regions of the brain while barely modulating activity at the target when constrained to safe currents for tACS and TI EFs in particular. Finally, it is suggested that electric fields off-target could generate conduction blocks, which can lead to a lack of neuronal response to additional inputs.

Discussion: This exploratory study demonstrates some of the challenges –such as off-target conduction blocks – to be considered if NIBS methods were applied for deep brain structure targeting when treating neuropsychiatric conditions in the future.

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