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Letter to the Editor

Transcutaneous electric currents to target the peripheral and central nervous system in children with attention deficit hyperactivity disorder

The possibility to indirectly modulate neural activity with transcutaneous nerve stimulation (TNS) provides a promising and exciting opportunity for clinicians to intervene with disease-related brain processes. The view that TNS can be safely applied for extended periods of time further contributes to its appeal. Together with the user-friendliness of the simulator device that allows for use outside the clinic makes TNS an attractive and potentially minimally invasive intervention for both therapists and patients.

The therapeutic potential of TNS in children (8–12 years) with attention-deficit hyperactivity disorder (ADHD) was recently demonstrated in a clinical trial (McGough et al., 2019). In that randomized double-blind, sham-controlled study, four consecutive weeks of nightly TNS (individual titrated intensity between 2 and 4 mA applied at a frequency of 120 Hz with a duty cycle of 30 s on/30 s off for approximately 8 h) resulted in significant improvements of clinician-rated ADHD symptoms and clinical global impression. The outcomes were framed in a hypothetical mechanism involving TNS-related excitation of the nucleus tractus solitarius, which relays signals to a broad set of cortical and limbic brain areas. Although this intriguing finding may open new treatment avenues in psychiatry, we would like to address a number of issues that in our opinion is important with respect to the applicability of TNS in young children.

Foremost, we have performed computational modelling and results indicate that TNS can have a direct stimulating effect on the frontal cortex rather than indirect excitation of the nucleus tractus solitarus as proposed by the authors. Results as depicted in Fig. 1 show that the electric field generated by TNS as low as 2 mA (peak-to-peak) can extend to the frontal cortex.

While our results cannot establish whether the electric field intensities are strong enough to have a biological effect, the estimated peak values found in our simulation appear sufficiently high (>0.3 V/m) to affect nerve tissue. Further empirical support comes from a study that found bi-frontal transcranial electric current stimulation applied in the ripple range (140 Hz) at 1 mA has an effect on processes associated with memory consolidation (Ambrus et al., 2015).

In agreement with the well-documented frontal cortex involvement in ADHD (McCarthy et al., 2014), it might be so that the effects to TNS are in fact caused by direct stimulation of the frontal cortex rather than the trigeminal nerve.

An additional issue that deserves to be taken into consideration is the current lack of knowledge on the physiological effects and safety of exogenous electric current stimulation during sleep. Prior studies have shown that children with ADHD more often experience sleep problems and that sleep problems may exert a causal and/or exacerbating effect on ADHD symptoms. Even though the authors report that TNS was well tolerated with minimal risks involved, significant increases in weight, pulse, fatigue, headache, and appetite were observed in the active versus the sham TNS group. In addition, Chi-square analyses on the reported side effects show that significantly ($p < .05$) more nightmares and drowsiness were reported in the active versus sham condition. This pattern of side effects indicates the presence of sleep disturbances in response to TNS.

Thirdly, the impact, either direct or indirect, of prolonged TNS on the young developing brain is currently not known. Lower levels of the inhibitory neurotransmitter gamma-amino-butyric acid in the frontal cortex in children as compared to adults (Cohen-Kadosh et al., 2015) could provide a biochemical basis for different physiological dynamics by which TNS produces its effects. Therefore, further insights into the effects of TNS on the young brain are necessary to determine whether short-term symptom improvements are not accompanied by homeostatic disturbances that have a long-term negative impact on, for example, neural plasticity.

In conclusion, TNS is a promising modulatory technique for the treatment of ADHD. However a better understanding of the physiological mechanisms and thereby safety in the young developing brain is fundamental before TNS can be considered a realistic therapeutic option for children and adolescents with ADHD, and other mental disorders.

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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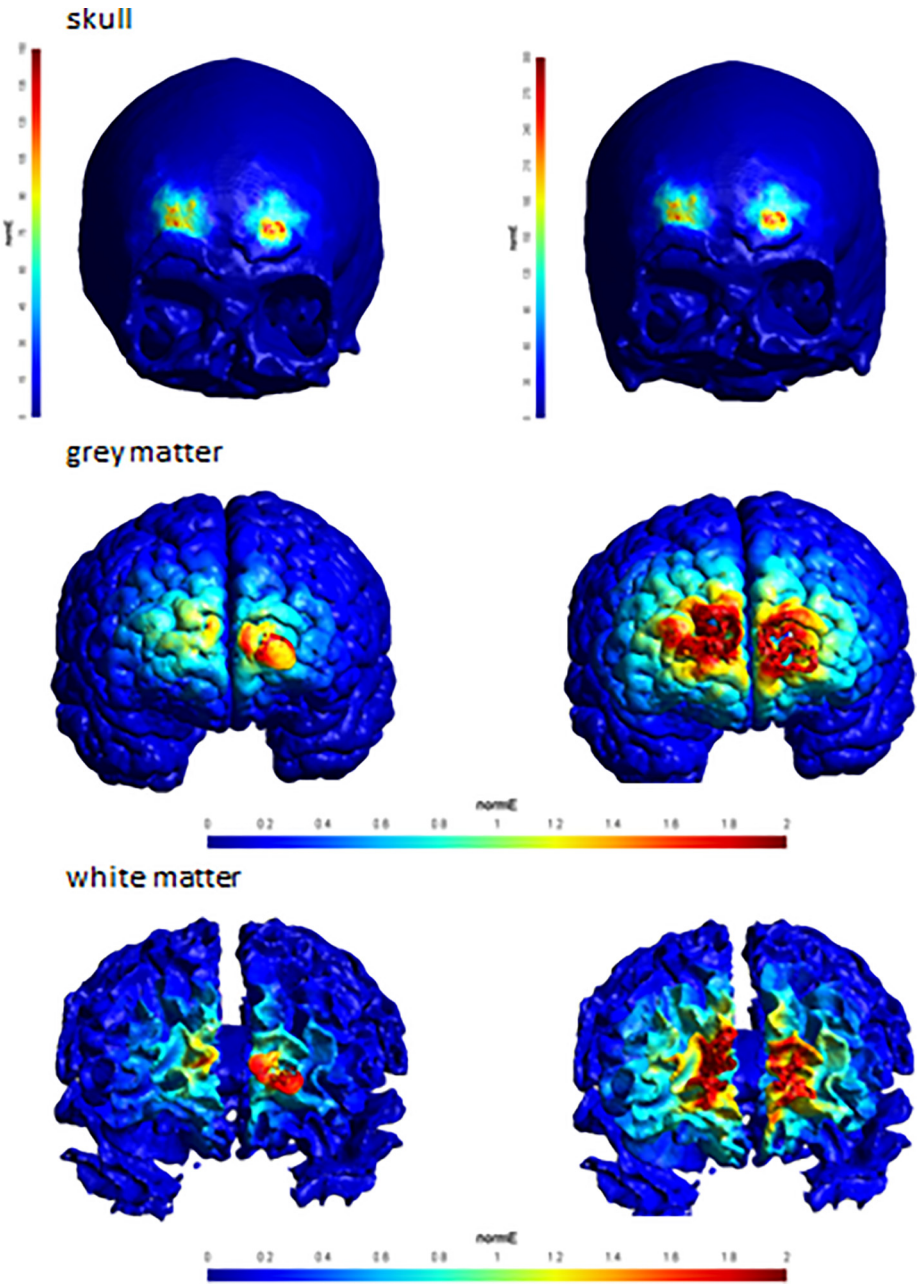

Fig. 1. The modelling was done with SimNIBS software (version 2.0.1) (Opitz et al., 2015) using an individual realistic tetrahedral head model created from a T1-weighted structural 3 T magnetic resonance image of a 10-year old boy provided in the dataset of the Brain Time study of Leiden University (Leiden, the Netherlands). Simulations on the head model were performed with two elliptical 1-mm thick electrodes (1.25-inch diameter) located over supraorbital foramen at intensities of 2 and 4 mA (peak-to-peak) TNS. NormE: V/m.

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