

# High frequency strong current tACS : a new dawn of non-drug therapy for patients with major depressive disorder

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**To cite:** Hu L, Li X, Zhou D, *et al.* High frequency strong current tACS : a new dawn of non-drug therapy for patients with major depressive disorder. *General Psychiatry* 2023;**36**:e101261. doi:10.1136/gpsych-2023-101261

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/gpsych-2023-101261>).

Received 27 July 2023

Accepted 01 November 2023



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A commentary on: Transcranial alternating current stimulation for treating depression: a randomized controlled trial.

By Wang H, Wang K, Xue Q, *et al.* *Brain*. 2022; 145(1):83-91. doi:10.1093/brain/awab252.

Major depressive disorder (MDD) is a common severe mental illness with recurring episodes. The most commonly used treatment is drug therapy, which is associated with a series of side effects and has an efficacy rate below 50%.<sup>1</sup> Non-invasive brain stimulation technique has been gradually applied in clinical practice. Transcranial alternating current stimulation (tACS), a form of non-invasive brain stimulation, is a light, wearable piece of equipment for cortical stimulation. It modulates cortical excitability and spontaneous brain activity by applying an electric current to the scalp, generating an alternating current that flows through the specified area between the stimulation electrodes. A recent study published in *Brain* proved the clinical potential of tACS stimulation for patients with MDD.

The study investigated the clinical safety and efficacy of tACS in first-episode, drug-naïve patients with MDD. The results showed that patients who received 20 daily 40 min, 77.5 Hz, 15 mA, one forehead and two mastoid sessions of active stimulation over four consecutive weeks achieved significantly higher remission rates than those who received sham stimulation. In addition, tACS treatment alleviated the depression state with lasting effects shown in 4 weeks of follow-up measurements; only some mild treatment-emergent adverse events were reported.<sup>2</sup> This is consistent with previous reports that tACS is associated with fewer side effects than antidepressants and electrochemotherapy (ECT).<sup>3</sup> On the other hand, tACS could induce phase locking of specific brain regions, such as neuronal spikes, at desired frequencies.<sup>4</sup> The efficacy of tACS treatment may vary based on different stimulation parameters, including

the stimulation target, frequency and current intensity.

The first novel aspect of this study is the utilisation of stronger electric currents. A current intensity of 15 mA was used in this randomised controlled trial, much stronger than what was commonly used in previous studies (often below 4 mA). In most cases, the lower current intensity is sufficient to effectively alleviate depressive symptoms.<sup>5</sup> In addition, strong electrical stimulation, such as electroconvulsive therapy, often leads to severe cognitive impairment in patients with MDD despite rapid relief of depressive symptoms.<sup>6</sup> Interestingly, the 15 mA current intensity in this study did not result in an increased occurrence of side effects. This prompts further investigation into whether a higher current intensity within the safe range can yield better results.

The second novel aspect of this study is the electrode placement and stimulation target for depression treatment. Given the importance of the frontal lobe in behavioural inhibition and emotional control, most tACS studies focused on the bilateral frontal lobe as the stimulation area, yielding positive outcomes. This study used three-spot stimulation instead of the conventional two-spot placement, with one anode placed in the middle of the forehead and two cathodes in the two mastoid regions. This configuration creates an anode-to-cathode current through the cerebral cortex, suggesting that different stimulation targets may have an antidepressant effect. However, it remains unclear whether other brain regions produce similar or better antidepressant effects.

The third novel aspect of this study is the frequency of stimulation. Conventionally, a gamma frequency of 40 Hz is used to alleviate depressive symptoms.<sup>7</sup> This study demonstrates that high-frequency gamma (77.5 Hz) stimulation can produce good antidepressant effects. This suggests that the gamma frequency band modulates specific brain shocks, enabling the patient's brain regions to regain their

original function. In addition, this oscillation provides a good sustained effect, which may be related to brain plasticity, though the exact mechanism of action remains unclear. In summary, controlled comparative studies are needed using combinations of different parameters, such as current intensities, electrode positions, and different electrode frequencies, to identify the optimal stimulation parameters for the treatment of depression.

Furthermore, cognitive impairment is one of the most frequent symptoms of MDD. Gamma oscillation is important for 'binding disparate cells' and memory function. Animal models revealed altered gamma power at the temporal lobe (eg, entorhinal cortices) at an early stage of disease. In addition, patients with cognitive impairment showed altered gamma oscillation in neural processing (eg, reduced early sensory gamma responses and delayed cognitive gamma responses). tACS applied to the temporal lobe can directly affect the hippocampus and entorhinal cortex, which are critical for cognitive changes.<sup>8</sup> However, it remains unclear whether strong current tACS of high-frequency gamma-band brain stimulation provides clinical benefits for cognition in patients with MDD.

This study has some limitations. First, the optimal stimulation protocol of tACS for patients with MDD and the rationale behind choosing 15 mA are unclear. Second, the applicability of the current results to all types of depression, including treatment-resistant depression and poststroke depression, is uncertain. Future studies are required to validate and extend current findings using different techniques (such as electroencephalography (EEG), functional near-infrared spectroscopy (fNIRS) and functional magnetic resonance imaging (fMRI)) in different MDD subgroups. Moreover, whether tACS combined with drugs or psychotherapy has a better effect is worth exploring.

In conclusion, Wang *et al's* study demonstrated the efficacy and safety of high-frequency gamma and strong current tACS in alleviating the symptoms of MDD. This novel stimulation approach may be

a new dawn of non-drug therapy for patients with MDD.

**Acknowledgements** The authors thank their department for its support.

**Contributors** LH, XL designed the letter and DZ and SW contributed equally to this letter, including writing and approval of the text for submission.

**Funding** The study was supported by the Basic Public Welfare Project of Zhejiang Province (LGF21H090008), Ningbo Medical Science and Technology Project (2019Y24), and Ningbo medical and health brand discipline (PPXK2018-08).

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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