Anodal Transcranial Pulsed Current Stimulation at Delta-Gamma range Frequencies: Effects on Corticospinal and Corticocortical Excitability

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Background: The effects of delta-gamma range anodal transcranial pulsed current stimulation (a-tPCS) on corticospinal excitability (CSE) and cortico-cortical excitability (CCE) remain unexplored. This study aimed to investigate the a-tPCS impact at 0.5, 1, 3, 5, 10, 25, and 80 Hz frequencies on CSE and CCE, as underlying mechanisms behind CSE changes, including inhibitory/facilitatory effects and potential stimulation side effects.

Gaps: (1) TPCS is a relatively new neuromodulatory technique with limited research on underlying mechanisms; (2) the effects of different frequencies of a-tPCS on CSE ; (3) the effects of different frequencies of a-tPCS on CCE; (4) and the effects of different a-tPCS frequencies on adverse effects.

Aims: (1) To investigate the effects of different frequencies of a-tPCS (0.5, 1, 3, 5, 10, 25, and 80 Hz) on CSE and CCE, including short intra-cortical inhibition (SICI), long intra-cortical inhibition (LICI), and intra-cortical facilitation; (2) To evaluate the possible side effects of these frequencies of a-tPCS.

Definition of terms: Transcranial pulsed current stimulation (tPCS) as a neuromodulation technique delivers unidirectional rectangular pulses at specific frequencies, defined by pulse duration (PD) and inter-pulse interval (IPI). It modulates brain activity through both **static polarisation** (shifting the resting membrane potential) and frequency-dependent **dynamic effects** (frequency-specific modulation of brain activity), potentially involving neural **entrainment** (synchronization of brain rhythms to external rhythmic stimulation) and neuroplasticity (Jaberzadeh et al., 2015). Thus, it has the potential to be considered as a complementary treatment for neurodegenerative disorders.

Materials and Methods

Study design: Double-blinded, randomised, counterbalanced crossover trial

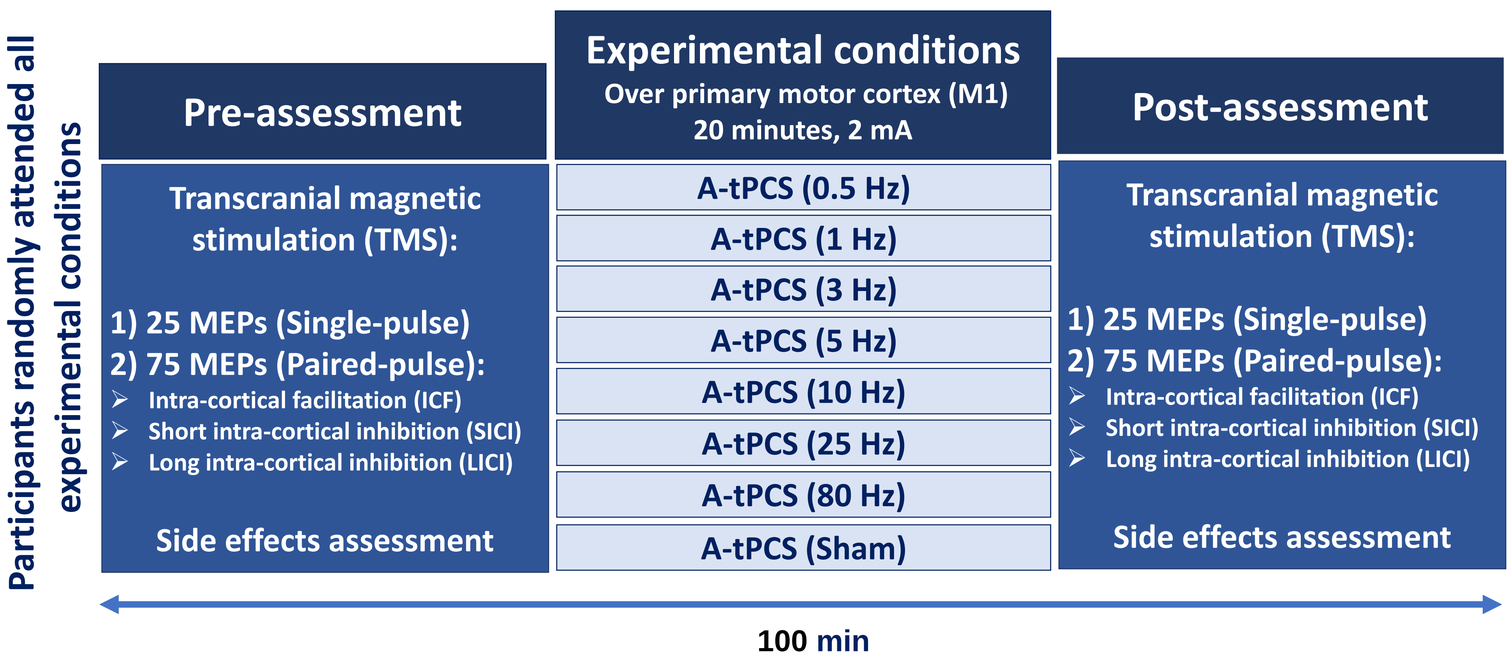

Figure 1. Study design. Double –blinded, randomized, counterbalanced crossover trail

Participants: 18 healthy volunteers (18-42 years-old) completed all experimental sessions with a minimum 48-hour washout period between sessions. This study approved by Monash University HREC (ID: 32335). All participants gave written informed consent. Data were anonymized and securely stored in line with the Declaration of Helsinki and the National Statement on Ethical Conduct.

Outcome measures:

- **TMS single-pulsed:** indicated CSE
- **TMS paired-pulse:** indicated CCE (ICF, SICI, and LICI)
- **Side effect assessment:** measuring tingling, itching, phosphenes, headache, and burning sensation

Statistical analysis: A parametric two-way ANOVA with post-hoc Benferoni has been applied for these assessments.

Results

Findings significantly ($p<0.05$) indicated that ≥1 Hz frequencies enhanced CSE, while at <1Hz decreased CSE. These changes were observed at 1Hz (31%), 5Hz (35.19%), 10Hz (64.58%), and 25Hz (44.82%) by increasing the ICF associated with glutamergic mechanism. However, the increase at 80Hz (27.66%) indicates a reduction in SICI associated with counter-regulatory effects on GABAergic mechanisms. The CSE reduction at 0.5Hz (-18.40%) was associated with increased SICI associated with $GABA_A$. All a-tPCS frequencies reported mild side effects, also 0.5 and 80Hz reported no phosphenes.

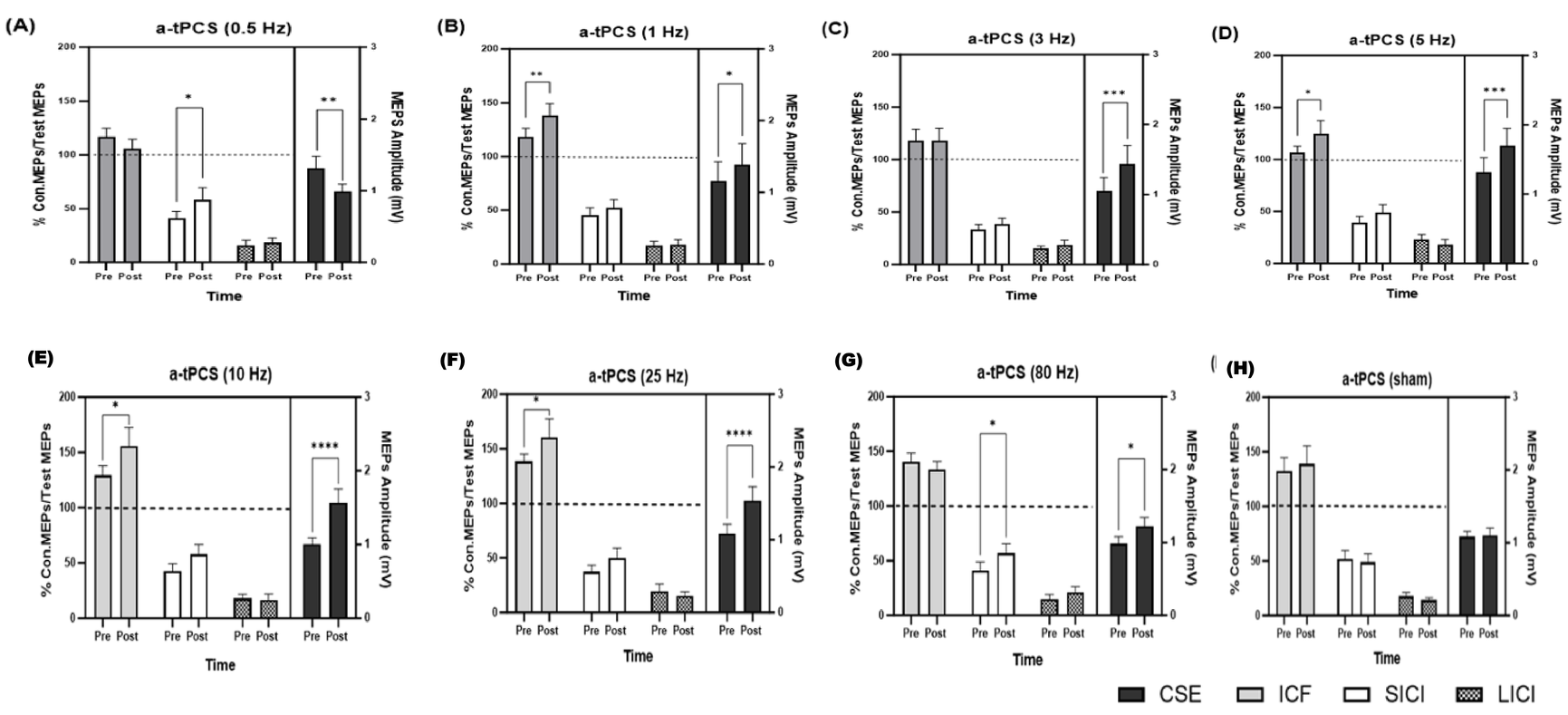

Figure2. The effects of different a-tPCS frequencies on CSE and CCE. a-tPCS at 0.5, 1, 3, 5, 10, 25, and 80 Hz was applied to assess its effects on ICF, SICI, and LICI, compared to sham stimulation. The dotted line at 100% indicates the baseline MEP amplitude (no conditioning stimulus). *p < 0.05; **p < 0.01; ** **p < 0.0001. Con.: Conditioned_test of averaged 25 MEPs, Test MEP: average of 25 MEPs 1mv

Significance

This study may guide the optimisation of neuromodulation therapies by refining tPCS parameters as a complementary treatment to enhance efficacy while reducing side effects in clinical situations.

Conclusions

Low-frequency a-tPCS (<1 Hz) induced LTD-like (long-term depression) effects, while higher frequencies (≥1 Hz) promoted LTP-like (long-term potential) mechanisms and enhanced ICF, indicating increased neuroplasticity. Notably, 0.5 Hz increased SICI, reflecting greater inhibition. Stimulation at 80 Hz showed counter-regulatory neuroplastic effects. Overall, frequency-dependent modulation of excitability was evident. Adverse effects were minimal, with 0.5 and 80 Hz showing no phosphenes, and other frequencies associated with only mild side effects