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Modulating positive self-referential processing by 40 Hz tACS in individuals with subthreshold depression: A double-blind, sham-controlled study

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A B S T R A C T

Background: A positive self-evaluation is essential to mental well-being. Despite of its importance, little is known how to modulate or enhance positive self-evaluation. Gamma-frequency (40 Hz) transcranial alternating current stimulation (tACS) has been shown to promote emotion regulation and memory, which may foster positive self-evaluations. Here, we investigated whether 40 Hz tACS over the medial prefrontal cortex (mPFC), a key brain region implicating self-referential processing, could enhance positive self-evaluation among individuals exhibiting subthreshold depression. We hypothesized that the 40 Hz stimulation would enhance self-evaluation.
Methods: Participants with subthreshold depression were screened using the Center for Epidemiological Studies Depression Scale Revised-10 item (CES-D-10). In a double-blind, randomized, sham-controlled, between-subjects experiment, sixty participants were randomly assigned to two groups: in the active stimulation group, 31 participants received 20-min session of 40 Hz tACS over the mPFC via high-density tACS. In the sham group, 29 participants received the sham stimulation over the same region. Before and after the tACS, participants completed the Self-Referential Encoding Task (SRET), which they endorsed and recalled positive and negative personality traits.
Results: We found a significant interaction among stimulation group, depressive symptoms, trait valence (positive or negative). Among participants who received the 40 Hz stimulation, higher levels of baseline depressive symptoms were associated with increased endorsement/recall of positive personality traits compared to the sham group ($p < 0.05$).
Conclusion: 40 Hz gamma tACS over the mPFC enhanced positive self-referential processing among individuals with subthreshold depression, an effect particularly evident among those with higher depressive symptoms. This effect highlights the potential therapeutic benefits of gamma-frequency stimulation in promoting positive self-evaluation among individuals with depression.

1. Introduction

Positive self-evaluations are fundamental for mental health and psychological resilience (Taylor and Brown, 1988). Having positive self-evaluation protects people from stress and adversity, and is associated with more effective coping strategies (Mann, 2004; Sedikides and Gregg, 2008). In contrast, a lack of positive self-evaluation disposes people to mood disorders such as depression (Alloy et al., 1990; Duyser et al., 2020; Obonsawin et al., 2017; Duyser et al., 2020, 2020; LeMoult et al., 2017; Weisenburger et al., 2024). Subthreshold depression, characterized by elevated depressive symptoms yet still below the diagnositic criteria for major depression disorder (MDD), shows heightened risks developing into MDD across different age groups (Lee et al., 2019; Zhang et al., 2023). Interventions targeting at ameoliarating depressive symptoms among this population can be particularly cost-effective and important to prevent future development into MDD. Given that a negative self-evaluation is a recognized risk factor for depression, interventions that enhance positive self-evaluation may aid in early prevention (Hards et al., 2020; Wood and Joseph, 2010). However, effective methods for modulating self-evaluations remains underexplored.

Neuroimaging evidence suggests that the medial prefrontal cortex (mPFC) is involved in self-referential and self-evaluative processing (Chavez et al., 2017; Lemogne et al., 2012; Levorsen et al., 2023). Thus, a plausible hypothesis is that modulating the mPFC can influence positive self-evaluation. However, a few studies employed transcranial direct current stimulation (tDCS) to modulate activity of the mPFC, yet found no significant tDCS effects on self-referential processing nor self-evaluation (Burden et al., 2021; Mainz et al., 2020). These results suggest that alternative neuromodulation methods shall be examined to

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modulate self-evaluation.

Unlike tDCS, which modulates cortical excitability using a constant direct electric current, transcranial alternative current stimulation (tACS) administers mild electrical current oscillating at a specific frequency, enabling modulation of neural oscillations that are associated with specific cognitive/emotional processes (Herrmann et al., 2013; Polanía et al., 2018). Self-referential processing often depends on coordinated oscillatory activity across cortical midline structures (Johnson et al., 2009; Northoff et al., 2006). Given that tACS directly engages neuronal circuits at specific frequencies, it offers a more refined approach for influencing the neural oscillatory mechanisms involved in self-evaluation. Here, we examined whether 40 Hz gamma tACS can modulate and enhance positive self-evaluation. Moreover, we used an High Definition(HD)-tACS setup, placing the central electrode at AFz, and four return electrodes at FP1, FP2, F1, and F2 according to the 10-10 EEG system. This HD-tACS setup allows us to target the MPFC with high focality (Davis et al., 2023; Miller et al., 2015; Sreeraj et al., 2020).

Emerging evidence shows that gamma frequency tACS benefits cognitive and emotional functions across various tasks/domains, such as it facilitates fluid intelligence in complex reasoning tasks, enhances working memory, improves long-term memory retention, and elevates positive mood among individuals with depression (Grover et al., 2022; Haller et al., 2020; Hoy et al., 2015; Nissim et al., 2023; Nomura et al., 2019; Reinhart and Nguyen, 2019; Santarnecchi et al., 2016, 2019; Strüber and Herrmann, 2020). Importantly, memory processes such as encoding and retrieval supports self-evaluation because they allow individuals to access and recollect self-descriptive events and semantic knowledge (Pauly et al., 2013). In addition, gamma power is associated with activity in the default mode network (e.g., mPFC) implicating self-referential processing (Iravani et al., 2024; Knyazev, 2013).

Importantly, the benefits of neuromodulation may depend on participants' cognitive/emotion states (Alagapan et al., 2016; Li et al., 2019). For example, when neuromodulation is implemented when participants engaged in relevant tasks, it benefits the targeted cognitive processing more than neuromodulation during rest without tasks (Andrews et al., 2011; Segrave et al., 2014). This benefit is likely due to the synchronization between exogenous neuromodulation and endogenous neural activity associated with the targeted cognitive processing (Bradley et al., 2022). In the current study, we leveraged this task-tACS synchrony design, by asking participants to view and give speeded motor responses to positive traits (see also Yao et al., 2024). This task thus ensures participants' attention and engagement with positive traits. We hypothesize this gamma tACS-task synchrony design, combined with the advantage of HD-tACS, will increase the efficacy of gamma tACS in enhancing positive self-evaluation as evidenced by higher self-endorsement and recall of positive traits.

2. Method

2.1. Participants

A total of 63 young adults (mean age years, 10 males) were recruited via university email circulars and advertisements. Participants were prescreened for depressive symptoms using the Center for Epidemiological Studies Depression Scale (CES-D-10, Björgvinsson et al., 2013). The exclusion criteria were as follows: a history of psychiatric disorders, a history of serious head injury or epilepsy; severe physical illnesses; alcohol or substance dependence; sleep disorders, such as insomnia or difficulty falling asleep; non-normal or uncorrected vision; the use of psychoactive medications, including sleeping pills; metallic implants such as pacemakers; a history of losing consciousness for more than 5 min; current head wounds or skin diseases; pregnancy or the possibility of being pregnant. Participants who met the inclusion criteria and those who scored $\geq$ 10 from the CES-D-10 (i.e., moderator or above depression, subthreshold depression) were included in the study (Björgvinsson et al., 2013).

After excluding participants who felt unwell and withdrew before the stimulation began (n = 2) and those who were not native Chinese speakers (n = 1), 31 participants were randomly assigned to the 40 Hz stimulation group (7 males, aged 21.4 $\pm$ 1.86), and 29 participants were assigned to the sham group (6 males, aged 20.9 $\pm$ 2.34). An independent samples *t*-test showed no significant age difference between the groups, $t(58) = 0.90$, $p = 0.37$. Our sample sizes (31 and 29 participants per group) align with previous studies targeting at mPFC modulating self-referential processing and self-reference memory (n = 14 to 25 participants per group, Mainz et al., 2020; Burden et al., 2021). All participants provided written informed consents before the commencement of the experimental tasks. The study was approved by the Human Research Ethics Committee of the University of Hong Kong (HREC Reference Number: EA230448).

2.2. Experimental design

The experiment employed a between-subjects design, as depicted in Fig. 1. Participants initially completed the Psychomotor Vigilance Task (PVT) to assess baseline vigilance levels.

Subsequently, participants completed a series of personality trait assessments. These assessments served as a cover story to enhance engagement with the subsequent SRET by leading participants to believe that the task would evaluate their self-perception based on these traits. The standardized questionnaires included the Rosenberg Self-Esteem Scale (RSES, Rosenberg, 1965), Narcissistic Personality Inventory (NPI, Ames et al., 2006), Big Five Inventory (BFI, John et al., 1991), Beck Depression Inventory-II (BDI-II, Beck et al., 1996), the Rumination on Sadness Scale (RSS, Conway et al., 2000)), State-Trait Anxiety Inventory (STAI, Spielberger, 1983), Barratt Impulsiveness Scale (BIS-11, Yang et al., 2007), Five Facet Mindfulness Questionnaire (FFMQ, Baer et al., 2006), Life Orientation Test-Revised (LOT-R, Scheier et al., 1994), and the Emotion Regulation Questionnaire (ERQ, Gross and John, 2003)).

Following the completion of these questionnaires, participants proceeded to the Self-Referential Encoding Task (SRET) to assess baseline, pre-tACS self-evaluation. The SRET consisted of three main components. In the **Binary Endorsement Task**, participants evaluated 80 personality traits—40 positive and 40 negative—for self-relevance through binary (yes/no) decisions. Each trait was presented on the screen for 800 ms, followed by 2 s response window during which participants were required to press either the left or right arrow key using two fingers of their dominant hand. The assignment of specific arrow keys was counterbalanced for each participant across two experimental blocks.

The **Continuous Rating Task** required participants to use the same set of trait words to provide continuous ratings based on each word's relevance and importance to their personality. Similar to the binary task, each trait was briefly displayed for 800 ms to remind participants of the word, ensuring consistent exposure time and encoding levels. Participants then had up to 8 s to provide their ratings, allowing for a more detailed self-evaluation compared to previous binary decision-making task. Within each trial, participant first rated the self-descriptiveness of the presented trait, followed by an assessment of its importance (Levorsen et al., 2023).

In the **Free-Recall Task**, participants were given 5 min to recall and type out as many traits words as possible. The words shall be from the prior two tasks. This recall measure provided an index of participants' positive self-perception: the more positive traits they recall, the more positive of their self-evaluation.

Following these pre-tACS baseline tasks, participants underwent two blocks of tACS, totaling 20 min (detailed in Section 2.3). Upon concluding the stimulation, participants completed a post-tACS questionnaire (Matsumoto and Ugawa, 2017) designed to document any immediate sensations or side effects experienced during stimulation. Responses were recorded using a standardized Likert scale ranging 1 (No discomfort) to 5 (Severe). They then repeated the PVT to assess any changes in vigilance levels post-tACS, followed by another 5-min

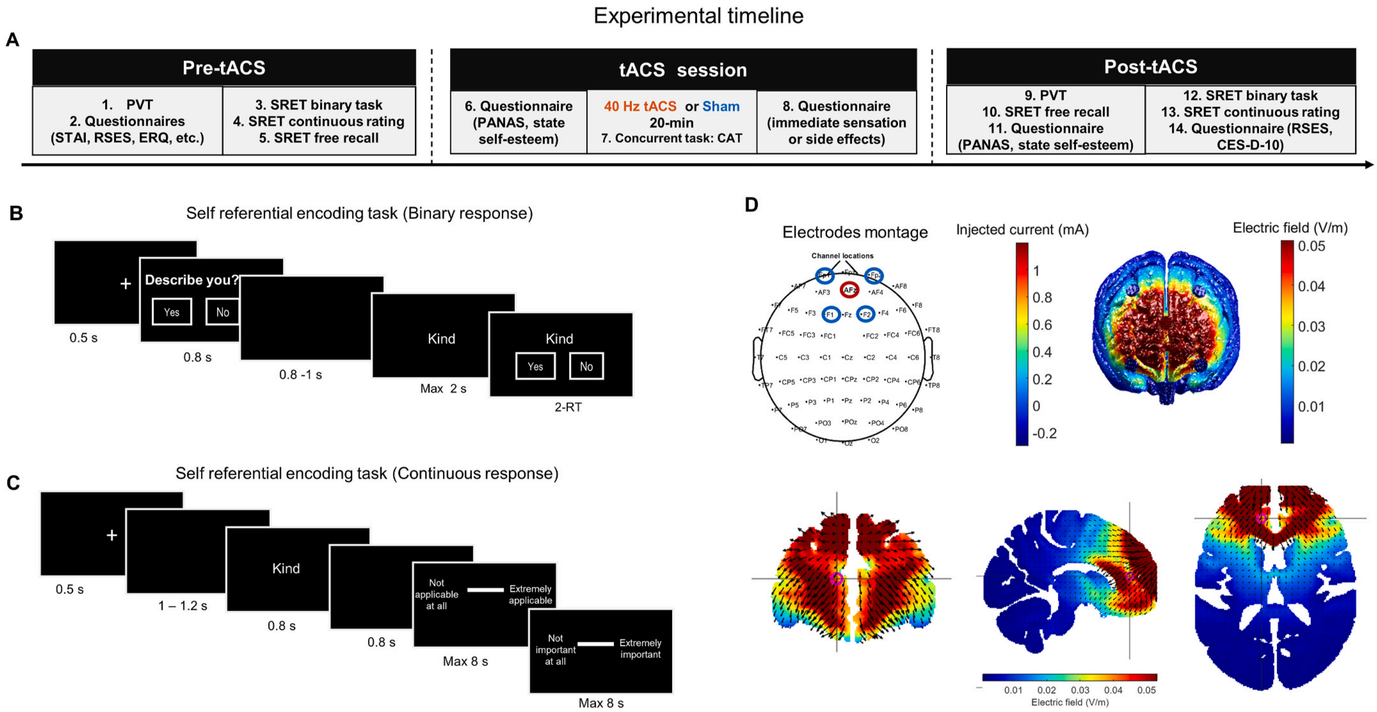

Fig. 1. An overview of the experiment procedure, experimental tasks and electric field modeling. A) Experimental procedure. Participants finished pre-tACS questionnaires and SRET tasks, followed by 20-min tACS, and post-tACS SRET tasks and questionnaires. B) Self referential encoding binary task. C) Self referential processing continuous rating task. D) Simulated electric field modeling of the tACS montage targeting the medial prefrontal cortex (mPFC), conducted using the ROAST toolbox for Matlab (V3.5, Huang et al., 2019). Upper panel: Placement of stimulation electrodes following the 10-10 international EEG system. Stimulation electrodes were positioned at AFz (target electrode, red circle), FP1, FP2, F1, and F2 (return electrodes, blue circles). Lower panel: Electric field magnitude simulation displayed on axial, coronal, and sagittal planes (left to right), with black arrows indicating current flow direction. The mPFC is visualized by setting the MNI coordinates to X = −10, Y = 50, Z = 12, marked by intersecting vertical and horizontal lines. tACS, transcranial alternating current stimulation; V/m, Volt per meter. STAI = State-Trait Anxiety Inventory; ERQ = Emotional Regulation Questionnaire (ERQ); RSES = Rosenberg Self-Esteem Scale (RSES).

Free-Recall Task to evaluate changes in memory performance. Participants were reassessed using the abbreviated Positive and Negative Affect Schedule (PANAS, Watson et al., 1988) and a state self-esteem measurement (Heatherton and Polivy, 1991) to detect any fluctuations in mood states and self-esteem levels immediately following the tACS.

Finally, participants completed the SRET's free recall, Binary Endorsement Task, and Continuous Rating Task to assess any changes in self-referential judgments. The experiment concluded with the administration of final questionnaires including Insomnia Severity Index (ISI) to assess subjective insomnia severity, CES-D-10 to assess depression symptoms and RSES to measure self-esteem. The last two assessments were designed to capture participants' mood and self-evaluation changes over the course of the study.

2.3. tACS protocol

We employed high-definition HD-tACS to modulate the neural activity in the medial prefrontal cortex (MPFC), a region implicated in self-referential processing and self-positivity bias (Fields et al., 2019; Northoff et al., 2006). The tACS was administered using a Soterix Medical 1 × 1 HD-tES stimulator and 4 × 1 HD-tES splitter (Soterix Medical Inc., New York, USA). The electrode montage consisted of one central electrode placed at AFz (Davis et al., 2023; Miller et al., 2015; Sreeraj et al., 2020), and four return electrodes positioned at FP1, FP2, F1, and F2, following the international 10–10 EEG system to target the MPFC with high focality. We also used computational modeling with the open-source pipeline i.e., Realistic vOlumetric Approach to Simulate Transcranial Electric Stimulation (ROAST, Huang et al., 2019) to confirm that the peak electric field in our tACS montage was centered over the medial prefrontal region (Fig. 1D). The stimulation frequency was set at 40 Hz to engage gamma-band oscillations. The electric current intensity was individually calibrated for each participant using a staircase procedure (Vossen et al., 2015; Wei et al., 2024), such that starting at 0.7 mA and increasing in 0.2 mA increments up to a maximum of 1.5 mA during a 2-min adjustment period. Participants were instructed to report any discomfort. The final intensity was determined when they reported a clear but tolerable sensation without phosphenes.

The study followed a randomized, double-blind, sham-controlled between-subject design. Participants were randomly assigned to either the active tACS group (40 Hz stimulation) or the sham tACS group. In the active group, participants received two consecutive blocks of stimulation, each lasting 10 min, totaling 20 min. There was no break between the two blocks; however, participants were provided with a 2-min reminder of the task instructions between the blocks to ensure task engagement. Each block began with a 30-s ramp-up period to minimize abrupt sensations. In the sham group, stimulation also began with a 30-s ramp-up to their individualized intensity at 40 Hz, then stopped with no further stimulation being delivered during the session. Due to the two-block structure, participants in the sham group received a total of 60 s of minimal stimulation. Both participants and experimenters who provide instructions were blinded to group assignments to ensure the validity of the results. The 20-min stimulation duration was selected based on previous studies demonstrating that this length of tACS effectively induces neural changes and modulates cognitive-affective processing (Grover et al., 2023; Kasten et al., 2016; Kasten and Herrmann, 2017). Additionally, this duration aligns with practical constraints of the experimental design, ensuring sufficient post-stimulation assessment without excessive participant fatigue or attentional drift.

During the tACS stimulation phase, we had participants engage in a concurrent cognitive task to enhance the efficacy of the stimulation, as previous studies have demonstrated that combing stimulation with an active task yields superior outcomes compared to the stimulation during

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rest (Alagapan et al., 2016; Li et al., 2019). Specifically, participants performed a modified Cue Approach Training Task (CAT, Schonberg et al., 2014), which involved viewing positive personality traits presented sequentially without making self-referential judgments. This task was intentionally designed to direct participants' attention to positive traits, aiming to facilitate subsequent positive self-referential processing in the SRET. Specifically, 40 positive trait words were presented randomly. For the first 10 min, half of these words were assigned to a "Go" condition, in which participants were required to press a button in response to a delayed visual cue associated with the trait. The remaining words were assigned to a "No-Go" condition, during which participants passively viewed the traits without responding. In the latter half of the stimulation phase, the assignments were reversed: words previously in the "Go" condition became "No-Go", and vice versa. Inter-trial intervals between trait words ranged from 5 to 7 s, designed to maintain participants' attention without causing excessive cognitive load.

In addition, during the stimulation session, participants rated their current feelings every 2.5 min on a scale from 1 to 100, assessing three specific items: "How satisfied are you with yourself overall?" (self-esteem), "How tense do you feel?" (relaxation), and "How fatigued do you feel?" (fatigue). This procedure yielded a total of eight measurements for each rating type, excluding the baseline assessment.

2.4. Statistical analysis

All statistical analyses were conducted using R software (Version 4.2.2., R Core Team (2020), n. d.). Baseline differences in personality measures between the two stimulation groups prior to tACS were assessed using independent t-tests on the questionnaire scores. Post-tACS PANAS and state self-esteem ratings were analyzed using analysis of covariance (ANCOVA), with pre-tACS scores as covariates to control for initial levels and isolate potential immediate stimulation effects. Additionally, CES-D-10 and RSES scores were compared between the groups using ANCOVA, with the baseline scores included as a covariate to examine changes throughout the study period.

In addition, self-reported measures of self-esteem, fatigue, and relaxation were collected at approximately 2.5-min intervals during the stimulation session. To compare the active tACS and sham groups over the course of the stimulation, consecutive ratings were averaged to provide measures at 5, 10, 15, and 20 min. A 2 (40 Hz vs. sham) $\times$ 4 (time points) mixed-design ANCOVA was performed to assess in these ratings with baseline rating and CES-D-10 score as covariates.

To examine how 40 Hz tACS modulates self-referential processing, we employed a series of separate 2 (between-subject, 40 Hz vs. sham) by 2 (within-subject, valene, positive vs. negative) mixed-design ANCOVAs on the following dependent variables: self-referential endorsement percentage, endorsement ratings, free-recall memory performance, and reaction times (RTs) during trait endorsement. We included pre-tACS baseline performance, and the baseline CES-D-10 depression scores as covariates, to control for individual differences in baseline performance and in baseline depression scores. We were particularly interested in examining how baseline depression levels and baseline performance might interact with stimulation group and valence on self-referential processing outcomes. Post-hoc tests were conducted following significant interactions and were corrected for multiple comparisons using the false discovery rate (FDR) method. When there were interactions between continuous factor (e.g., CESD), simple slope analysis was further conducted (high: +1 SD, average: mean value, and low: −1 SD) to examine the direction and significant interaction effects.

3. Results

3.1. Participants were blind to group assignment

Eighty-five percent of the participants responded that they believed they received the stimulation (26/31 from the active group, 25/29 from the sham group), indicating successful blinding to group assignments. Independent Mann-Whitney U Tests were performed for each side effect and the results indicated that there were no statistically significant differences between the groups for any of the assessed side effects (all *p*-values >0.057).

3.2. No personality questionnaire score differences between two groups

Independent t-tests conducted on baseline personality questionnaire scores indicated no significant differences between the two stimulation groups. Similarly, ANCOVA analyses of post-tACS PANAS and state self-esteem ratings, controlling for pre-tACS scores, revealed no significant group differences. Further analyses of CES-D-10 and RSES scores at the conclusion of the study also demonstrated no significant differences between the groups (all *p*-values >0.241). Descriptive statistics were presented in Supplement Tables 1 and 2

3.3. Dynamic ratings during tACS did not differ across two groups

The mixed 2 (40 Hz vs. sham) by 4 (timepoints, 5, 10, 15, and 20 min) ANCOVA showed that no significant group differences were found for self-reported measures of self-esteem, relaxation or fatigue ratings across time points (all $ps > 0.05$). These results suggest that the 40 Hz tACS did not significantly alter dynamic self-esteem, relaxation, or fatigue ratings compared to sham group. Descriptive statistics were presented in Supplement Table 3.

3.4. 40 Hz tACS modulated positive self-referential endorsements and memory of free recall

An ANCOVA was conducted to examine the effects of 40 Hz tACS on post-tACS free recall of positive and negative self-referential traits, with baseline free recall performance and baseline depression scores as covariates. A significant three-way interaction was found among group (40 Hz tACS vs. sham), valence (positive vs. negative traits), and depressive symptoms (CES-D-10 scores) on the percentage of traits recalled, $F\ (1, 104) = 5.10$, $p = 0.026$. Specifically, higher depressive symptoms were associated with a greater percentage of positive traits recalled in the 40 Hz tACS group compared to the sham group, $\beta = 0.02$, SE $= 0.01$, $p = 0.015$. No significant difference was observed for the recall of negative traits, $\beta = -0.001$, SE $= 0.01$, $p = 0.886$ (Fig. 2A).

A similar pattern emerged for self-referential endorsements and endorsement ratings. Significant three-way interactions were found among group, valence, and depressive symptoms for both the percentage of endorsements, $F\ (1, 104) = 4.65$, $p = 0.033$ (Fig. 2B), and endorsement ratings, $F\ (1, 104) = 4.12$, $p = 0.045$ (Fig. 2C). Post-hoc comparisons reveal that in the 40 Hz tACS group, participants with higher depressive symptoms endorsed more positive personality traits ($\beta = 0.02$, SE $= 0.01$, $p = 0.047$), and assigned higher ratings to those endorsements compared to the sham group ($\beta = 1.15$, SE $= 0.42$, $p = 0.008$). Importantly, this effect was specific to positive traits; no such enhancement was observed for negative traits (endorsements: $\beta = -0.01$, SE $= 0.01$, $p = 0.482$; endorsement rating: $\beta = -0.60$, SE $= 0.40$, $p = 0.137$).

Importantly, simple slopes analysis revealed that for positive traits, higher levels of depressive (+1 SD CES-D-10 score) was significantly related to higher recall ($\beta = 0.06$, SE $= 0.03$, $p = 0.05$, Fig. 2D), endorsement ($\beta = 0.10$, SE $= 0.05$, $p = 0.031$, Fig. 2E), and endorsement rating ($\beta = 5.10$, SE $= 2.05$, $p = 0.014$, Fig. 2F) of positive traits for 40 Hz than sham group, but not for the mean or lower levels of depressive symptoms (−1 SD, all $ps > 0.11$).

Together, these interactions indicate that the gamma tACS effect on self-evaluation was moderated by both depressive symptoms and trait valence: 40 Hz tACS enhanced positive self-evaluation or self-referential processing among those with higher depression symptoms.

Note that all significant interactions involving the group and valence

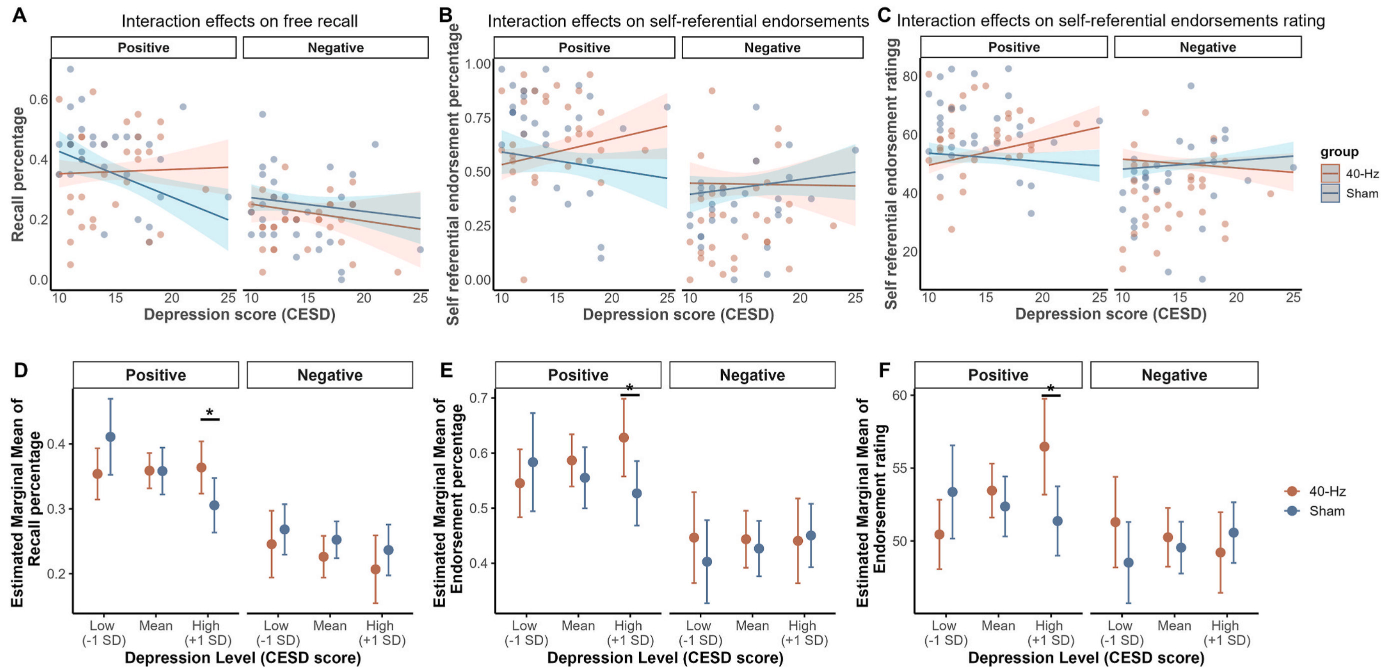

Fig. 2. Interaction effects on self-referential processing by group, trait valence, and the level of depression symptoms. A) The relationship between CES-D (depression) scores and the percentage of positive (left panel) and negative (right panel) traits recalled, separated by stimulation group (40 Hz tACS vs. sham). Each point represents an individual's recall percentage, and shaded areas indicate the standard error of the mean across individuals. B) The relationship between depression scores and self-referential endorsement rates for positive and negative items across two groups: 40 Hz stimulation (red) and sham (blue). Shaded regions indicate the standard error of the mean across individuals. C) The association between depression scores and self-referential endorsement ratings is shown for positive and negative traits across the 40 Hz tACS and sham conditions. Each data point represents individual ratings, and the shaded regions indicate the standard error of the mean across individuals. D-F) Estimated marginal means of the recall (D), endorsements (E), and endorsement rating (F) by CES-D-10 levels, group, and valence condition. Each point represents the estimated marginal mean of the outcome variable for 40-Hz and sham groups at three CESD levels: Low (−1 SD), Mean, and High (+1 SD), under both positive and negative valence conditions. Error bars represent the 95 % confidence intervals around the estimated marginal means. CESD: Center for Epidemiological Studies Depression Scale. SD: standard deviation.

factors were reported in detail. Main effects and other interactions that did not involve the group and valence were summarized and presented in Supplement Tables 4–6 (for recall, binary endorsement, and endorsement rating).

3.5. 40 Hz tACS did not modulate RTs of endorsements or importance rating of personality traits

An ANCOVA controlling for baseline endorsement RTs revealed no significant main effects or interactions among group, valence, and depressive symptoms on reaction times (all $ps > 0.05$). Furthermore, there were no significant effects on the importance ratings of personality traits (all $ps > 0.05$).

4. Discussion

Subthreshold depression, characterized by negative self-evaluation, presents a significant risk for the onset of clinical depression yet remains an under-studied population. Investigating potential interventions to enhance self-evaluations among subthreshold depression can be important as it may prevent further progression into major depression disorder (Buntrock et al., 2017; Tadić et al., 2010). Our findings bridge this gap by showing that 40 Hz transcranial alternating current stimulation (tACS) applied over the medial prefrontal cortex (mPFC) may benefit individuals with subthreshold depression. Further simple slope analysis indicated that, compared to the sham group, participants in the 40 Hz tACS group with higher depressive symptoms benefited more than those with lower depressive symptoms, as they endorsed and recalled more positive traits, rated these positive traits as more self-descriptive.

A central finding in this study is that the 40 Hz gamma tACS enhanced positive self-evaluation, providing further evidence that gamma tACS can effectively modulate cognitive and emotion processes (Haller et al., 2020; Nissim et al., 2023). Moreover, our results partially align with prior research demonstrating that gamma tACS can ameliorate depressive symptoms (Haller et al., 2020), such that low self-esteem or the lack of positive self-evaluation is a core depressive symptom (Hilbert et al., 2019; Zheng et al., 2014).

Importantly, our findings reveal that individual differences in baseline depressive symptoms significantly influenced the relationship between 40 Hz tACS and self-evaluation (Schutter et al., 2023; Soleimani et al., 2023). Specifically, in the 40 Hz tACS group, participants with higher baseline depressive symptoms not only endorsed more positive traits but also rated these traits as more self-descriptive, and they recalled more positive traits in the post-tACS tasks. This selective enhancement in positive self-evaluation among individuals with subthreshold depression indicate that these vulnerable individuals are particularly responsive to gamma tACS, and may derive greater therapeutic benefits from the 40 Hz tACS. This finding underscores the role of individual baseline characteristics in influencing the effectiveness of tACS interventions, aligning with prior research on state-dependent neuromodulation (Bradley et al., 2022). A fruitful direction to pursue is to target individuals with specific depressive symptom profiles, making 40 Hz tACS a potentially valuable tool for precise and early intervention.

Our study advances previous research on neuromodulation and self-referential processing in three key ways. First, unlike previous studies that often utilized tDCS, we used 40 Hz gamma-band high-definition tACS. The 40 Hz gamma is a frequency known to modulate high-order cognitive functions like working memory, long-term memory retention, fluid intelligence, and mood regulation (Grover et al., 2022; Haller et al., 2020; Hoy et al., 2015; Reinhart and Nguyen, 2019; Santarnecchi et al., 2016). The precision of gamma tACS may have allowed us to more effectively target neural oscillation associated with positive self-evaluation, addressing limitations in earlier tDCS study that produced inconsistent results in modulating self-referential processing (Mainz et al., 2020). Second, unlike protocols where stimulation is administered during passive resting state, we applied tACS during an active task specifically designed to engage positive traits processing. This task-specific approach likely enhanced the synchronization between exogenous neurostimulation and endogenous neural activity involved in positive self-evaluative processing (Alagapan et al., 2016; Andrews et al., 2011). Prior research suggests that neuromodulation with active task engagement can amplify task-relevant brain activity (Li et al., 2019). Thus, this task-tACS synchronization design may explain our observed tACS-induced improvements in positive self-evaluations. Third, our study focused on participants with subthreshold depression, a population particularly vulnerable to depression. We found that those with higher baseline depressive symptoms derived greater benefits from 40 Hz tACS, emphasizing the importance of state-dependent effects and the need for personalized neuromodulatory interventions based on individual symptom severity.

Our findings invite future research to understand the benefits of neuromodulation on self-evaluation and possibly on depressive symptoms. First, while we showed the immediate benefits of 40 Hz tACS, our previous work suggests that 40 Hz tACS can have long-lasting benefits in enhancing optimistic biases (Yao et al., 2024). These results provide converging evidence that 40 Hz tACS may modulate valence-dependent and self-referential processes (optimism and positive self-evaluation) that are strongly associated with depression (Korn et al., 2014). Future research shall investigate whether multiple sessions of tACS can bring long-lasting benefits in alleviating depressive symptoms. Second, the mechanisms underlying the benefits of 40 Hz tACS remains to be addressed. While our electric field modeling suggests that the HD-tACS montage effectively targeted the medial prefrontal cortex (mPFC), we acknowledge that we do not have direct neural evidence confirming the stimulation effects in this region. The 40 Hz tACS could amplify gamma power across broader, interconnected neural networks (Mencarelli et al., 2022). Future research employing concurrent neuroimaging techniques, such as fMRI, could provide real-time validation of mPFC engagement during 40-Hz tACS to validate whether the effects are driven by localized modulation within the mPFC or by more widespread network-level effects. Relatedly, emerging neuromodulation methods like Temporal Interference (TI) stimulation offer a promising alternative for reaching deeper brain regions with greater focality (Esmaeilpour et al., 2021; Guo et al., 2023). Future research shall consider employing TI stimulation to optimize targeted neuromodulation for self-evaluation. Third, although we employed a sham-controlled condition, it remains unknown whether neuromodulation at other frequencies—such as theta or alpha tACS—or alternative stimulation techniques like tDCS could achieve similar benefits on self-evaluation. Prior work (Liu et al., 2023) has shown that tDCS can reduce negative memory biases among individuals with subthreshold depression along with decreased alpha power. Given the role of different frequency bands in memory, attention, and emotion regulation, future research should systematically compare the effects of theta, alpha, and gamma tACS, as well as tDCS-based approaches, to determine their efficacy in modulating positive self-evaluations. Forth, while our findings indicate that 40-Hz tACS enhances positive self-evaluation in the SRET, it remains an open question whether this effect generalizes to other self-evaluation tasks. Given that self-referential processing biases are closely linked to depression (LeMoult et al., 2017), our choice of SRET was driven by its established sensitivity in assessing self-evaluation distortions. However, future studies could employ other related tasks, such as self-referntial matching paradigms (Sui and Humphreys, 2015) or self-report self--evaluation questionnaires (Donnellan et al., 2015), to determine whether our tACS protocol may improve positive self-evaluation more broadly.

In conclusion, our findings highlight the potential of 40 Hz gamma, high-definition tACS targeting at mPFC in enhancing positive self-evaluations. Notably, benefits of neuromodulation are particularly evident among individuals with higher subthreshold depressive symptoms. Future studies shall investigate how to optimize tACS protocols for its therapeutic applications in mood disorders such as depression.

CRediT authorship contribution statement

Ziqing Yao: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Pui Yi Tu:** Formal analysis, Data curation. **Xibo Zuo:** Writing – review & editing, Investigation, Data curation. **Jinwen Wei:** Writing – review & editing, Formal analysis, Data curation. **Xiaoqing Hu:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Data and code availability

Data and code that support the findings of this study are available in the Open Science Framework: https://osf.io/2vdcp/?view_only=e55ba61131c3450d89d7db0a5e7ddc05.

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2025.04.004.

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