

Behavioral and neural modulation effects of transcranial pulse stimulation of the dorsal cingulate cortex and anterior insula cortex in healthy adults: A prospective, randomized, sham-controlled trial

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Abstract

Background

Transcranial pulse stimulation (TPS) is a novel non-invasive brain stimulation technique with promising neuromodulation effects. No studies have examined target-specific deep brain TPS. This study assessed whether TPS of the dorsal anterior cingulate cortex (dACC) and anterior insular cortex (AIC) modulates risk-taking behavior and brain circuits in healthy participants.

Methods

Seventy-five healthy adults were randomized in this subjects/raters-blind study to 10 sessions of active dACC-TPS, active AIC-TPS, or sham-TPS over 2 weeks. Balloon Analog Risk Task (BART), a psychological measure of risk-taking behavior with high ecological validity, was assessed at baseline, midpoint (Week 1), and endpoint (Week 2). Resting-state functional connectivity (rsFC) was measured at baseline and endpoint.

Results

Most participants experienced mild-to-moderate adverse events, primarily tingling and pain at the stimulation site. The overall dropout rate was 4%. Significant interactions emerged in the BART: dACC-TPS significantly decreased average pumps (average pumps on all trials), AIC-TPS significantly increased adjusted average pumps (average pumps on trials where the balloon did not burst), and sham showed no change. Target-specific rsFC changes were observed following active stimulation versus sham: dACC-TPS predominantly enhanced rsFC of dACC and AIC with precuneus, parietal, and occipital cortices, whereas AIC-TPS decreased rsFC of AIC with striatum.

Conclusions

Ten sessions of dACC-TPS and AIC-TPS are feasible and safe. dACC-TPS decreased risk-taking behavior, whereas AIC-TPS increased it. Bidirectional, target-specific rsFC changes were observed. Future large-scale studies with online neuroimaging or neurophysiological investigations are needed to confirm short- and long-term efficacy and clarify underlying mechanisms.

Trial Registration

ClinicalTrial.gov Identifier NCT06635161.

Background

Transcranial pulse stimulation (TPS) is a novel, non-invasive brain stimulation (NIBS) technique that utilizes shock waves to modulate brain (1). Derived from extracorporeal shock wave therapy, its hypothesized biophysiological mechanism relies on “mechanotransduction”—converting strong, short-duration mechanical forces into physiological and biochemical responses (2) that promote neurogenesis and angiogenesis (3, 4). Recent animal studies revealed that TPS induced immediate calcium activity in neurons, increased c-Fos expression in the murine cortex, reorganized functional connectivity across brain networks, and enhanced overall cerebral blood volume (5, 6).

TPS can target both cortical and deeper brain regions (up to 8 cm) with a spatial resolution of several millimeters (7). Its feasibility, safety, and therapeutic efficacy have been investigated in healthy adults (7–9) and in several clinical populations, including Alzheimer's disease (AD) (5, 7, 10–12), major depressive disorder (MDD) (13), mild cognitive impairment (14, 15), Parkinson's disease (16, 17), attention deficit hyperactivity disorder (18), and autism spectrum disorder (19), demonstrating promising therapeutic and neural effects, especially in AD (10) and MDD (13). However, existing trials have applied stimulation broadly across multiple brain regions or to specific superficial cortical areas, leaving the target-specific effects of deep-brain TPS unexplored.

The dorsal anterior cingulate cortex (dACC) and anterior insular cortex (AIC) are core nodes of the salience network (SN), which identifies relevant stimuli to guide attention and behavior (20). SN dysfunction is implicated in depression, anxiety, autism spectrum disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and schizophrenia (21–24). In depression, insular hypoconnectivity within SN and hypoconnectivity between the dACC node of SN and the precuneus node of the attention circuit have been noted, with insular hypoconnectivity inversely related to symptom severity (25, 26). This dysfunctional connectivity may contribute to anxious avoidance and negative bias in depression (23). Structural neuroimaging evidence further supports the central role of the dACC and AIC in mental health. A landmark meta-analysis of over 15,000 individuals with various psychiatric disorders identified reduced grey matter volume in the bilateral AIC and dACC as the sole structural abnormalities common across psychiatric disorders (27). Several low-intensity transcranial focused ultrasound (tFUS) studies have explored neuromodulation of the dACC and AIC in healthy adults. Stimulation of each region was found to affect Pavlovian biases, with dACC stimulation increasing perseveration bias and AIC stimulation reducing learning bias (28). In addition, AIC stimulation can inhibit pain processing and increase heart-rate variability (29). Notably, the same tFUS protocol can induce opposite neural effects—excitatory or inhibitory—depending on the target site, as reflected by changes in resting-state functional connectivity (rsFC) and neurotransmitter levels (30, 31).

Given the research gap and the relevance of the dACC and AIC to mental disorders, this study aimed to assess the feasibility, safety, and modulatory effects of TPS targeting these deeper regions in healthy adults. To probe AIC and dACC functions, the Balloon Analog Risk Task (BART), a psychological measure of risk-taking, was assessed, given its well-established relevance to both regions (32). Notably, aberrant risk-taking has been documented across a range of psychiatric disorders, including MDD (33), anxiety (34), schizophrenia (35), and substance use disorders (36). Based on prior evidence from tFUS studies,

we hypothesized that dACC- and AIC-TPS would affect BART performance and induce target-specific rsFC changes. Our goal was to establish foundational evidence for TPS as a tool for deep brain neuromodulation and to identify potential therapeutic targets for mental disorders.

Methods

Study overview

A subjects/raters-blind, sham-controlled randomized trial was conducted to investigate the effects of TPS of AIC and dACC. The study was conducted at The Hong Kong Polytechnic University between August 2024 and December 2025. The trial protocol was approved by the Institutional Review Board of The Hong Kong Polytechnic University (Reference No: HSEARS20240319006) and registered at ClinicalTrials.gov (Identifier: NCT06635161). The present study reports findings from a subset of data collected as part of the registered trial. Additional results from the full trial will be reported elsewhere. Eligible healthy participants were randomized to receive active dACC-TPS, active AIC-TPS, or sham vertex-TPS for 10 sessions over 2 weeks. BART performance was evaluated at baseline, midpoint (before the sixth session), and endpoint (after the final session). Structural magnetic resonance imaging (sMRI) and resting-state functional magnetic resonance imaging (rs-fMRI) were performed at baseline and endpoint.

Participants

Seventy-five healthy participants aged 18–65 years with the ability to understand and follow instructions were recruited via advertisement on billboards in the Hong Kong Polytechnic University campus. Exclusion criteria were: intracranial metal implants; corticosteroid use within 6 weeks; pregnancy/breastfeeding; standard NIBS/MRI contraindications (e.g., brain surgery, pacemaker, deep brain stimulation, intracranial metallic particles); prior TPS experience; color blindness; neuroscience background; or any neurological/psychiatric disorders. Eligible participants were enrolled in the study after obtaining written informed consent. The study complied with the Declaration of Helsinki (37).

Randomization and allocation concealment

Participants were randomized 1:1:1 to the three arms using computer-generated tables with a block size of 15. Each participant received a unique randomization ID corresponding to their assigned target. Sealed opaque envelopes with group allocations were prepared and maintained by the TPS operator throughout the study.

TPS procedure and blinding

Ten TPS sessions were applied over two weeks (five sessions per week). Targets in the bilateral dACC, bilateral AIC, and vertex were identified using neuronavigation based on each participant's sMRI (Fig. 1). Each session consisted of 1,000 pulses (500 per hemisphere for the AIC or dACC, and 1,000 for the vertex) delivered at 4 Hz with an energy flux density of 0.2 mJ/mm^2 . The left AIC (lAIC), right AIC (rAIC), left dACC (ldACC), right dACC (rdACC), and vertex were predefined as 15-mm-radius spheres centered at the following MNI coordinates, based on the Yeo atlas (38, 39): lAIC ($x = -41, y = 6, z = 3$), rAIC ($x = 44, y = 9, z = 2$), ldACC ($x = -4, y = 26, z = 45$), rdACC ($x = 7, y = 30, z = 40$), and vertex ($x = 0, y = -30, z = 60$). These spheres were transformed into each participant's individual T1-weighted space. However, because the TPS system's display interface is limited to a 30-mm penetration depth, the target spheres were repositioned outward along the skull-normal direction to the 30-mm display depth for visualization purposes. Specifically, adjusted target voxels were calculated to match the TPS display at a penetration depth of 30 mm. Adjusted 15-mm-radius spheres were then created as target zones on the individual T1-weighted image, centered at the center of mass of all adjusted target voxels. Critically, this repositioning preserves the energy trajectory toward the original MNI-transformed coordinates, ensuring that the actual stimulation targets (the MNI-derived coordinates) remain on the same pathway and are accurately stimulated despite the display limitation. For AIC targeting, a 6.6-mm gel cushion was used to achieve a focus depth of 15.4–71.4 mm; no cushion was used for dACC targeting (focus depth: 22–78 mm). Sham stimulation over the vertex used an air-filled cushion within the handpiece, producing auditory feedback without effective energy delivery. Adverse events were assessed using a predefined checklist after each session, and participants were instructed to report any additional symptoms.

The TPS operator was not blinded due to the need to know stimulation targets to perform TPS. Participants, however, remained blinded to the study hypothesis and design (partial information) (40): they were informed they would receive stimulation but not about specific targets or the sham-control condition. In addition, their lack of a neuroscience background precluded them from linking the stimulation sites to their corresponding brain functions. This ensured effective blinding throughout the study. Since participants also self-administered tasks and questionnaires, maintaining their blinding was critical to minimizing bias in subjective outcomes.

Psychological measurement

BART assessed the AIC and dACC involvement in risky decision-making (32). Participants inflated a virtual balloon, earning HKD 0.6 per pump but risking explosion, resulting in loss of trial earnings. Participants could stop pumping at any time to cash out accumulated earnings. The task included 30 trials (max 12 pumps each), with explosion probability increasing from 2% to 90% per pump (41). Risk-taking was quantified using three measures: average pumps (average pumps across 30 balloons, including both burst and non-burst balloons), adjusted average pumps (average pumps for non-burst balloons only), and the number of explosions.

MRI measurements

At baseline and endpoint, participants received a 6-minute sMRI scan using a Siemens 3T MAGNETOM Prisma system equipped with a 64-channel head coil. Standard scanning parameters were TR/TE = 2300/2.98 ms, flip angle = 9°, field-of-view (FOV) = 240 x 256 x 208 mm, voxel size = 1 x 1 x 1 mm. An 8-minute rs-fMRI scan was also performed. During this scan, participants were instructed to relax with their eyes open and to fixate on a cross displayed on the screen, allowing their minds to wander without focusing on specific thoughts. Rs-fMRI was acquired using single-shot gradient-recalled echo planar imaging with TR/TE = 607/32 ms, FOV = 220 x 220 x 160 mm, voxel size = 2.5 x 2.5 x 2.5 mm, 64 slices (slice thickness = 2.5 mm), interleaved acquisition, and a simultaneous multislice acceleration factor of 8.

Statistical analysis

An intention-to-treat analysis was performed using linear mixed models (LMM) for their flexibility, missing-data handling, and statistical power. The model included Group, Time, and Group-by-Time interaction as fixed effects, with participants as random effects. When a significant Group-by-Time interaction was detected, within-group post hoc comparisons were conducted to examine pre-to-post changes separately for each group. In the absence of a significant interaction, significant main effects were further explored: a significant main effect of Time was decomposed using within-group pairwise comparisons across time points, whereas a significant main effect of Group was examined using between-group post hoc comparisons. All post hoc tests were corrected for multiple comparisons using Bonferroni.

Rs-fMRI analyses were conducted using SPM12 and RESTplus v1.28 (42) in MATLAB 2023a. Preprocessing included realignment, spatial normalization, spatial smoothing (6-mm full width at half maximum kernel), detrending, nuisance covariates regression (removal of motion confounds, white matter, and cerebrospinal fluid signal), and bandpass filtering (0.01–0.08 Hz). Voxel-wise seed-based rsFC analyses were performed with seeds placed in the stimulation targets: bilateral AIC (MNI coordinates: lAIC: x = -41, y = 6, z = 3; rAIC: x = 44, y = 9, z = 2) and dACC (MNI coordinates: ldACC: x = -4, y = 26, z = 45; rdACC: x = 7, y = 30, z = 40) (38, 39). rsFC was calculated as Pearson correlation coefficients between the time series of each seed and those of all other voxels, and then converted to z-scores (zFC) for group-level analysis. Paired t-tests were conducted to test the pre-post changes within individual groups. Correlation analyses were then conducted to examine the relationship between significant pre-post changes in rsFC and BART performance within each group. For group-level analyses, statistical significance was set at a cluster-level familywise error rate (FWE) or false discovery rate (FDR) < 0.05.

Results

Participants characteristics

A total of 80 healthy participants were recruited, of whom 75 were included in the study. Five participants were excluded before the start of the first TPS session: four declined participation, and one

had incidental findings on the baseline sMRI scan. Of the 75 participants included, 72 completed the 2-week experiment. Two participants in the AIC group dropped out due to adverse events (headaches), and one in the dACC group withdrew for personal reasons unrelated to the study procedures. In addition, improper data storage resulted in completely random missing data: baseline BART data from one participant in the dACC group, and endpoint BART data from one participant in the AIC group. Of the enrolled 75 participants, 28 (37.3%) were males; the age was 23.44 ± 7.85 (mean $\pm$ SD) years, and the years of education were 15.47 ± 2.04 (mean $\pm$ SD). Baseline characteristics were comparable across groups (Table 1).

Table 1
Baseline characteristics of participants (n = 75)

Variable		AIC-TPS (n = 25)	dACC-TPS (n = 25)	Sham-TPS (n = 25)	p value
Male (n, %)		9, 36%	6, 24%	13, 52%	0.807
Age (y), mean (SD)		23.16 (8.47)	23.84 (7.12)	23.32 (8.21)	0.951
Education (y), mean (SD)		15.08 (1.89)	16.12 (1.81)	15.20 (2.30)	0.142
Baseline BART	Average Pumps (n), mean (SD)	4.77 (0.67)	5.05 (0.69) [n = 24] [#]	4.66 (0.95)	0.204
	Adjusted average pumps (n), mean (SD)	4.78 (0.77)	5.06 (0.89) [n = 24] [#]	4.78 (1.06)	0.409
	Exploded balloons (n), mean (SD)	12.88 (3.68)	15.08 (3.09) [n = 24] [#]	13.72 (4.50)	0.133

AIC: anterior insula cortex; TPS: transcranial pulse stimulation; dACC: dorsal anterior cingulate cortex; BART: balloon analog risk task. [#]: sample size after excluding completely random missing data due to storage issues.

BART

For the average pumps, a significant interaction effect was found ($F = 2.786$, $p = 0.029$) without significant main effects of Time ($p = 0.059$) or Group ($p = 0.790$). Post-hoc analyses revealed a significant decrease in the dACC group from baseline to Week 2 (mean difference = 0.362; 95%CI = 0.075 to 0.648; $p_{\text{corrected}} = 0.008$; Cohen's $d = 0.61$), whereas no significant within-group changes were observed in the AIC or sham groups (Fig. 2a).

For the adjusted average pumps, a significant interaction effect ($F = 2.674$, $p = 0.035$) was found, with no significant main effect of Time ($p = 0.417$) or Group ($p = 0.951$). Post-hoc analyses showed a significant increase in the AIC group from baseline to Week 2 (mean difference = -0.335; 95%CI = -0.655 to -0.015;

$p_{\text{corrected}} = 0.037$; Cohen's $d = 0.41$), while no significant within-group changes were found in the dACC or sham groups (Fig. 2b).

For the number of exploded balloons, no significant interaction effect ($p = 0.147$) or main effect of Group ($p = 0.557$) was found; however, a significant main effect of Time ($F = 14.128$, $p < 0.001$) was detected. A significant decrease in the dACC (mean difference = 3.130; 95%CI = 1.177 to 5.084; $p_{\text{corrected}} < 0.001$; Cohen's $d = 0.77$) and sham groups (mean difference = 2.172; 95%CI = 0.249 to 4.096; $p_{\text{corrected}} = 0.021$; Cohen's $d = 0.54$) were found after 2-week TPS. In addition, the AIC group showed a transient decrease at the midpoint (mean difference = 2.172; 95%CI = 0.214 to 4.131; $p_{\text{corrected}} = 0.024$; Cohen's $d = 0.53$), which was reversed at Week 2 (Fig. 2c).

Rs-fMRI findings

Of the 72 completers ($n = 24$ dACC, $n = 23$ AIC, $n = 25$ sham), all underwent endpoint MRI. Seven fMRI datasets were excluded due to poor alignment or normalization quality, leaving 66 participants ($n = 23$ dACC, $n = 21$ AIC, $n = 22$ sham) with both baseline and endpoint fMRI data for analysis.

- Seed-based rsFC changes following TPS

Following dACC stimulation, a significant increase in rsFC was found between the bilateral dACC and bilateral precuneus, cuneus, superior parietal and occipital cortex, and right angular cortex; and between ldACC and right dorsolateral prefrontal cortex (rDLPFC) (Table 2 and Fig. 3). No decrease in dACC-seeded rsFC was found following dACC stimulation.

Table 2
Rs-fMRI results displaying dACC-seeded clusters with a significant enhancement following dACC stimulation.

dACC group (n = 23)	Paired t-test (post > pre) ($P_{FWE-corr} < 0.05$)					
	Cluster No.	Brain regions	T (P value)	k	Peak MNI coordinates, x y z	AAL for the peak MNI
rdACC-seeded	Cluster 1	Bilateral precuneus; Bilateral cuneus; Bilateral superior parietal gyrus; Bilateral superior occipital gyrus; Right angular gyrus	6.01 ($P_{FWE-corr} < 0.0001$; $P_{FDR-corr} < 0.0001$)	322	9-72 51	Precuneus_R
ldACC-seeded	Cluster 1	Bilateral precuneus; Bilateral cuneus; Bilateral superior parietal gyrus; Bilateral superior occipital gyrus; Right angular gyrus	6.73 ($P_{FWE-corr} < 0.0001$; $P_{FDR-corr} < 0.0001$)	387	9-72 51	Precuneus_R
	Cluster 2	Right dorsolateral prefrontal cortex	5.60 ($P_{FWE-corr} = 0.035$; $P_{FDR-corr} = 0.081$)	69	24 12 57	Frontal_Sup_R

Rs-fMRI: resting-state functional magnetic resonance imaging; dACC: dorsal anterior cingulate cortex; AAL: automated anatomical labelling; MNI: Montreal Neurological Institute; L: left; R: right.

Following AIC stimulation, a significant decrease in rsFC was found between the bilateral AIC and right putamen; between the right AIC and left caudate and putamen; between the lAIC and the right caudate,

pallidum, supramarginal gyrus, and superior temporal gyrus (Table 3 and Fig. 3). No increase in AIC-seeded rsFC was found following AIC stimulation.

Table 3

Rs-fMRI results displaying AIC-seeded clusters with a significant reduction following AIC stimulation.

AIC group (n = 21)		Paired t-test (post > pre) ($P_{\text{FDR-corr}} < 0.05$)				
	Cluster No.	Brain regions defined by AAL	T (P value)	k	Peak MNI coordinates, x y z	AAL for the peak MNI
rAIC-seeded	Cluster 1	Caudate_L; Putamen_L	6.74 ($P_{\text{FWE-corr}} < 0.0001$; $P_{\text{FDR-corr}} = 0.001$)	143	-18 18 18	Caudate_L
	Cluster 2	Putamen_R	6.18 ($P_{\text{FWE-corr}} = 0.002$; $P_{\text{FDR-corr}} = 0.002$)	109	24 15 3	Putamen_R
IAIC-seeded	Cluster 1	Putamen_R; Pallidum_R; Caudate_R	6.04 ($P_{\text{FDR-corr}} = 0.002$; $P_{\text{FWE-corr}} = 0.007$)	109	24 15 3	Putamen_R
	Cluster 2	SupraMarginal_R; Temporal_Sup_R	5.60 ($P_{\text{FDR-corr}} = 0.027$; $P_{\text{FWE-corr}} = 0.050$)	62	60 - 39 33	SupraMarginal_R

Rs-fMRI: resting-state functional magnetic resonance imaging; AIC: anterior insular cortex; AAL: automated anatomical labelling; MNI: Montreal Neurological Institute; L: left; R: right.

Following sham stimulation, no significant changes were observed in dACC- or AIC-seeded rsFC, compared to the baseline.

To determine whether the observed rsFC changes reflected target-specific neuromodulation rather than a non-specific global stimulation effect, three exploratory analyses were conducted: (1) AIC-seeded rsFC changes following dACC stimulation; (2) dACC-seeded rsFC changes following AIC stimulation; (3) primary visual cortex (V1)-seeded rsFC changes following dACC-, AIC-, and sham-TPS (with the left V1 as a control region; MNI coordinates: x = -10, y = -91, y = 13 (43)). The results showed that dACC stimulation significantly increased the rsFC of AIC with several brain regions, including bilateral precuneus, right superior parietal gyrus, etc. (see Additional file 1, Table S1 and Figure S1). No significant

changes in dACC-seeded rsFC were observed following AIC stimulation, nor were there any significant V1-seeded rsFC changes after dACC, AIC-, or sham-TPS.

- Association between pre-post changes in rsFC and BART performance

Correlation analyses revealed no significant linear correlations between dACC-seeded rsFC and the BART performance (average pumps and exploded balloons) following dACC stimulation (see Additional file 1, Table S2). For AIC stimulation, changes in the rsFC between rAIC and left caudate and putamen showed a positive correlation with changes in BART adjusted average pumps ($r = 0.435$, $p_{\text{uncorrected}} = 0.049$) (see Additional file 1, Table S3). However, this correlation did not survive correction for multiple comparisons.

Integrity of Blind

Participants were blinded to the sham-controlled design, so it was unfeasible to ask them to guess their group assignment. Instead, they were asked to report subjective perceptions of TPS effects post-experiment. Among completers, one dACC-TPS participant and four sham-TPS participants reported performance improvement. Interestingly, three AIC-TPS participants and one dACC-TPS participant reported increased risk-taking willingness during the post-stimulation BART, while one sham-TPS participant reported reduced aggression during the post-stimulation BART.

TPS safety

Mild-to-moderate adverse events were reported by all AIC-TPS participants (100%), 96% (24/25) of dACC-TPS, and 72% (18/25) of sham, primarily tingling and pain at the stimulation site during stimulation. Nearly all symptoms resolved spontaneously within 12 hours without medication, except that one participant in the AIC group reported pain and headache (VAS = 6) after stimulation, which temporarily affected sleep but resolved spontaneously within two days. Detailed information on adverse events is provided in Table 5.

Table 5
Adverse events that occurred during the experimental period

	AIC-TPS (n = 25)	dACC-TPS (n = 25)	Sham vertex-TPS (n = 25)
	Number of participants reporting each adverse event during stimulation (%)		
Tingling [#]	21 (84%)	18 (72%)	2 (8%)
Pain [#]	9 (36%)	5 (20%)	5 (20%)
Pressure sensation [#]	3 (12%)	7 (28%)	2 (8%)
Striking sensation [#]	3 (12%)	10 (40%)	3 (12%)
Sourness [#]	NA	1 (4%)	NA
Dizziness	3 (12%)	3 (12%)	3 (12%)
Sleepiness	NA	2 (8%)	2 (8%)
Numbness [#]	6 (24%)	4 (16%)	1 (4%)
Headache	3 (12%)	2 (8%)	1 (4%)
Heating [#]	NA	1 (4%)	1 (4%)
Tinnitus	NA	3 (12%)	1 (4%)
Blurred vision	NA	2 (8%)	1 (4%)
Numbness in the arms/legs/hands	NA	1 (4%)	NA
Vibration in the ears	1 (4%)	NA	1 (4%)
Nausea	NA	1 (4%)	NA
Pain around the ears	NA	1 (4%)	NA
Neck pain	NA	1 (4%)	2 (8%)
Pain in the temple	NA	1 (4%)	NA
Muscle tightness in the face	NA	NA	1 (4%)
	Number of participants reporting each adverse event after stimulation (%)		
Headache	4 (16%)	NA	NA
Dizziness	1 (4%)	1 (4%)	2 (8%)

	AIC-TPS (n = 25)	dACC-TPS (n = 25)	Sham vertex-TPS (n = 25)
	Number of participants reporting each adverse event during stimulation (%)		
Pain [#]	3 (12%)	NA	1 (4%)
Tingling [#]	2 (8%)	NA	1 (4%)
Sleepiness	NA	NA	1 (4%)
Numbness in the arms/hands/toes	NA	NA	1 (4%)
Insomnia	1 (4%)	NA	NA

AIC-TPS: transcranial pulse stimulation over the bilateral anterior insula cortex; dACC-TPS: transcranial pulse stimulation over the bilateral dorsal anterior cingulate cortex; Sham vertex-TPS: sham transcranial pulse stimulation over the vertex; NA: not applicable. [#]: at the stimulation site.

Discussion

This study demonstrates that 10 sessions of TPS of dACC and AIC are feasible, safe, and effective in non-invasively modulating risk-taking behaviors and target-specific resting-state brain circuits in healthy adults.

We observed bidirectional behavioral effects of TPS of the dACC and AIC. Specifically, TPS of the dACC reduced risk-taking behavior, whereas TPS of the AIC increased it, as indicated by BART performance. These target-specific modulatory effects are consistent with a recent tFUS study, which reported that dACC-tFUS increased perseveration bias, while AIC-tFUS attenuated learning bias (28, 44, 45). This correspondence may reflect the distinct functional roles of dACC and AIC within the SN: the dACC appears to be more engaged in processing external environmental signals, while the AIC is more sensitive to internal interoceptive signals (28). This extrinsic-intrinsic divergence may also account for the different patterns of target-specific rsFC changes induced by external stimulation such as TPS.

In contrast to a previous single-session TPS study that failed to observe behavioral effects (9), our findings suggest that multiple sessions are required to induce behavioral changes. This phenomenon likely reflects the physiobiological mechanism underlying TPS, which may involve neurogenesis and angiogenesis driven by mechanotransduction—for instance, through altered protein expression or vascular growth that supports neuronal function (3, 4, 46, 47). Based on our clinical findings, we speculate that such physiobiological processes may require sufficient time to accumulate before they manifest as measurable behavioral outcomes.

Task-based fMRI studies have implicated both the dACC and AIC involvement in the BART, supporting their roles in performance monitoring, salience detection, and reward processing during risky decision-making (32, 48). In alignment with our behavioral findings, we also observed bidirectional, target-specific TPS-induced rsFC changes following dACC and AIC stimulation, compared with sham stimulation. Specifically, dACC-TPS enhanced dACC-seeded rsFC, consistent with findings from a tFUS study (31), whereas AIC-TPS reduced AIC-seeded rsFC with the striatum. Previous studies have established rsFC profiles for the dACC and AIC. The dACC exhibits positive rsFC with fronto-parietal regions and the DLPFC, a pattern linked to sensorimotor and higher-order cognitive functions (21). The AIC, in turn, shows positive rsFC with the precuneus and superior temporal cortices, facilitating the integration of attention, homeostatic, and emotional salience detection processes (49), and has also been linked to the striatum, including the putamen, caudate, and globus pallidus, which is a key node of the core reward network (50, 51). Against this known baseline, our findings suggest that dACC-TPS strengthens coupling between the SN and default mode network, as well as with the frontoparietal control and attention networks (23), whereas AIC-TPS weakens the AIC—core reward network connectivity, which has been negatively associated with impulsivity in healthy adults (52). However, it should be noted that these observed target-specific rsFC changes were not linearly correlated with the behavioral changes, which aligns with our previous TPS study in MDD (13). This may be possibly due to limited power, multifactorial behavioral changes (e.g., inter-individual psychosocial variability and placebo effects—factors not fully captured by rsFC measures alone), or nonlinear relationships.

Prior TPS studies have reported both increases and decreases in rsFC following stimulation. For example, enhanced global efficiency within the cortical sensorimotor network was observed after somatosensory cortex-TPS in healthy adults compared with sham stimulation (8). Upregulated global efficiency in the dorsal attention network was also found following whole-brain stimulation in old adults with AD compared to the baseline (10). Enhanced rsFC of multiple depression-relevant brain circuits was observed following active left DLPFC stimulation in adults with MDD compared with the sham stimulation (13). Conversely, down-regulation of rsFC (compared to the baseline) within the limbic system following whole-brain stimulation predicted improved global cognition in participants with mild cognitive impairment (15). These bidirectional, region-specific neural effects, observed across studies, underscore the need for further investigation into the neural mechanisms underlying TPS.

Study limitations

This study has several limitations. First, the majority of participants were highly educated undergraduates, which limits the generalizability of our findings. Second, long-term efficacy remains unknown after ten sessions of dACC- and AIC-TPS. Third, target engagement during stimulation was not directly assessed; however, the distinct rsFC changes observed across two deep target regions support effective neuromodulation of subcortical structures. Fourth, the TPS parameter space—including frequency, intensity, and dosage — has not been systematically investigated. Fifth, although TPS offers a lateral spatial resolution of 5.3 mm (5), a 4–5 mm lateral deviation (7) and a 56 mm axial spread (5) should be considered in precision targeting, as these may affect regions beyond the intended target.

Sixth, the absence of significant linear correlations between behavioral and neuroimaging outcomes leaves the neural mechanisms of TPS effects uncertain.

Conclusion

Two-week dACC- and AIC-TPS were feasible and safe. Preliminary findings suggest that dACC-TPS decreases risk-taking behavior, whereas AIC-TPS increases it. Differential rsFC changes were observed for dACC- and AIC-TPS, supporting the target-specific neuromodulatory effects of TPS in deeper brain regions. Larger future studies are needed to confirm the short- and long-term efficacy of deep-brain TPS. Moreover, online neuroimaging/neurophysiological investigations are essential for examining the precision of target engagement, mechanisms of action, and temporal dynamics across a multidimensional space of behavioral and neuroimaging/neurophysiological parameters.

Abbreviations

TPS

transcranial pulse stimulation

dACC

dorsal anterior cingulate cortex

AIC

anterior insular cortex

BART

Balloon Analog Risk Task

rsFC

resting-state functional connectivity

NIBS

non-invasive brain stimulation

AD

Alzheimer's disease

MDD

major depressive disorder

SN

salience network

tFUS

transcranial focused ultrasound

sMRI

structural magnetic resonance imaging

rs-fMRI

resting-state functional magnetic resonance imaging

MNI

Montreal Neurological Institute

lAIC
left anterior insular cortex
rAIC
right anterior insular cortex
ldACC
left dorsal anterior cingulate cortex
rdACC
right dorsal anterior cingulate cortex
FOV
field of view
LMM
linear mixed model
FWE
family-wise error
FDR
false discovery rate
rDLPFC
right dorsolateral prefrontal cortex
V1
primary visual cortex

Declarations

Ethics approval and consent to participate

The trial protocol was approved by the Institutional Review Board of The Hong Kong Polytechnic University (Reference No: HSEARS20240319006). All the included participants were enrolled in the study after obtaining written informed consent. The study complied with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing Interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Qin reported receiving nonfinancial support for operator training and travel cost coverage from the AMS Company outside the submitted work. Dr Kranz reported receiving travel cost coverage and/or speaker honoraria from Roche, Pfizer, Orphan Pharmaceuticals AG, HealthLink, Academy of Brain Stimulation, and Storz Medical outside the submitted work. Dr Padberg is a member of the European Scientific Advisory Board of Brainsway Inc., Jerusalem, Israel, and the

International Scientific Advisory Board of Sooma, Helsinki, Finland and reported receiving speaker's honoraria from Mag&More GmbH, Brainsway Inc., Jerusalem, Israel, and the neuroCare Group outside the submitted work. His lab has received support with equipment from neuroConn GmbH, Ilmenau, Germany, and Mag&More GmbH and Brainsway Inc., Jerusalem, Israel, outside the submitted work.

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Author Contribution

PPQ: conceptualization, investigation, data curation, methodology, writing- original draft. IKC: investigation, data curation, writing- review & editing. TTL: conceptualization, supervision, writing- review & editing. MJ: supervision, data analysis, writing- review & editing. RLK: training, data analysis, writing- review & editing. BBZ: supervision, writing- review & editing. AWX: supervision, writing- review & editing. SXW: supervision, writing- review & editing. VL: supervision, writing- review. JL: supervision, writing- review. TY: supervision, writing- review; BKHC: supervision, writing- review. TOB: supervision, writing- review. FP: supervision, writing- review. GSK: conceptualization, supervision, writing- review & editing, funding support. All authors read and approved the final manuscript.

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Availability of data and materials

The data are available from the corresponding author upon reasonable request.

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Figures

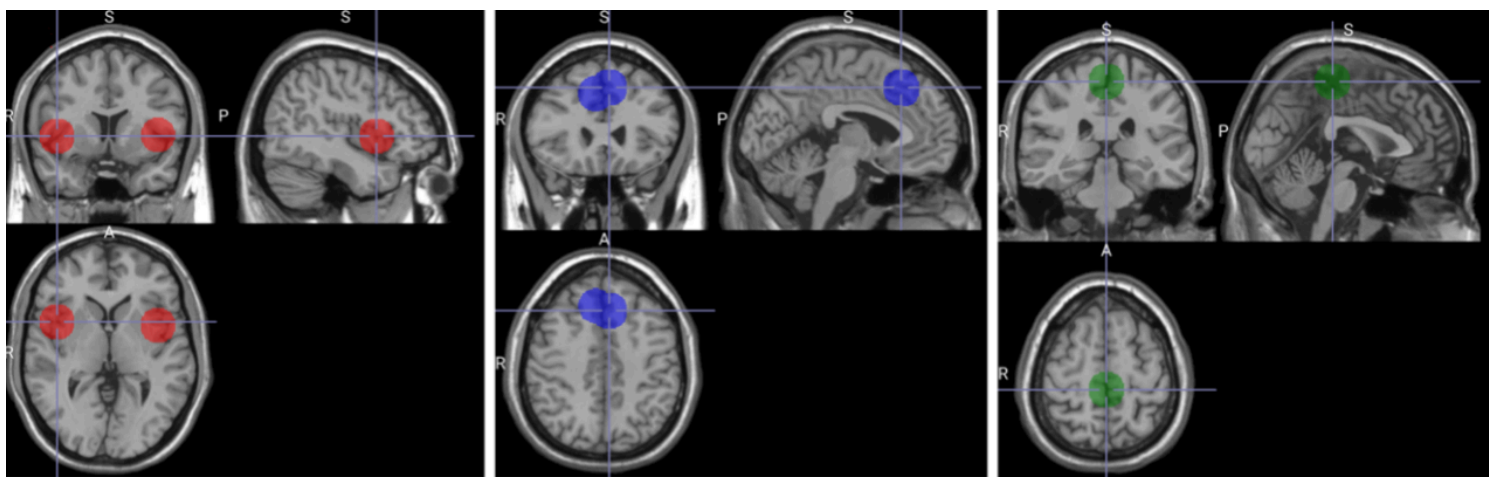


Figure 1

Stimulation targets. Left panel: bilateral anterior insular cortex (red); middle panel: bilateral dorsal anterior cingulate cortex (blue); right panel: vertex (green).

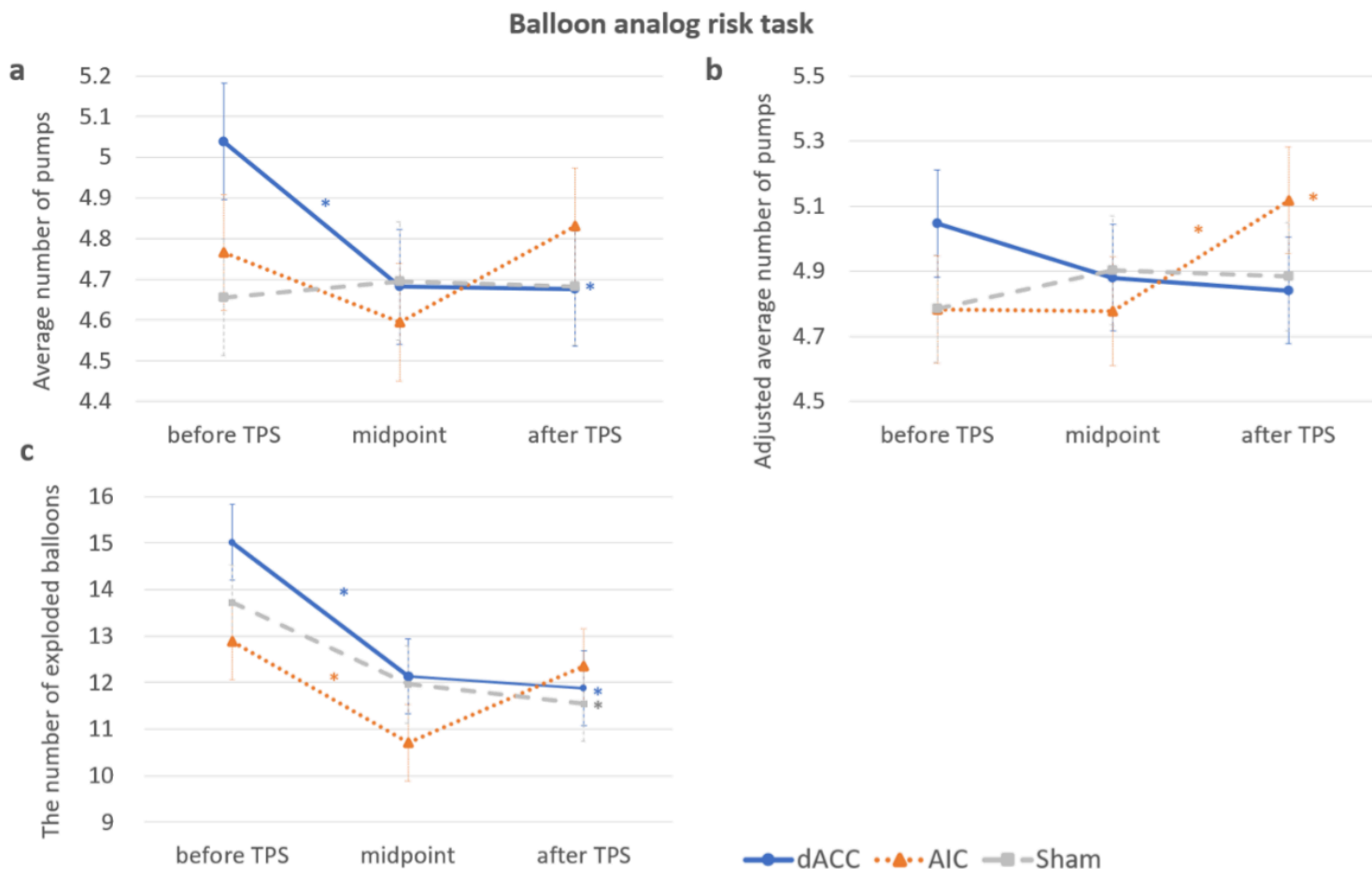


Figure 2

Changes in performance of the Balloon Analog Risk Task in the individual groups during the experimental period.

The blue dots, orange triangles, and grey squares indicate the mean values in the dACC, AIC, and sham groups, respectively; The bars indicate the standard errors. *: p-value < 0.05 after Bonferroni correction. a: the average number of pumps: the blue asterisks indicate the within-group difference between the baseline and midpoint, and between the baseline and the endpoint in the dACC group; b: the adjusted average number of pumps: the orange asterisks indicate the within-group differences between the baseline and midpoint, and between the baseline and the endpoint in the AIC group; c: the number of exploded balloons: the asterisks indicate the within-group differences between the baseline and midpoint, and between the baseline and the endpoint in the dACC group; the within-group difference between the baseline and the endpoint in the sham group; the within-group difference between the baseline and midpoint in the AIC group.

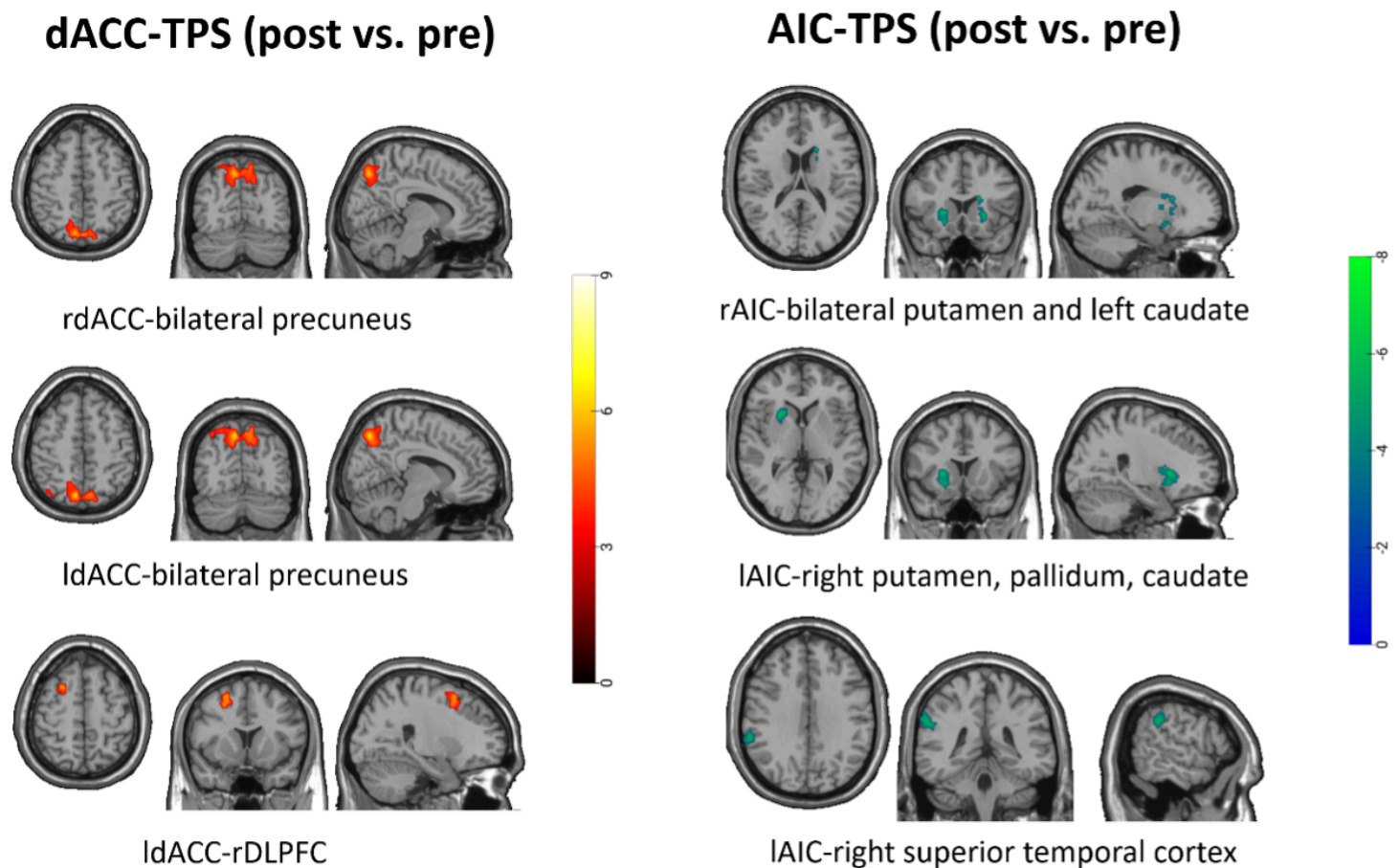


Figure 3

Changes in the target-seeded rsFC following 12-session TPS. Left: increases in the dACC-seeded rsFC following dACC-TPS: (1) upper panel (rdACC-seeded cluster 1 with a cluster size of 322, $T = 6.01$, cluster-level false discovery rate [FDR]-corrected $P < 0.0001$, peak MNI coordinates: $x = 9, y = -72, z = 51$): the bilateral precuneus, cuneus, superior parietal gyrus, superior occipital gyrus, and right angular gyrus; (2) middle panel (ldACC-seeded cluster 1 with a cluster size of 387, $T = 6.73$, cluster-level FDR-corrected $P < 0.0001$, peak MNI coordinates: $x = 9, y = -72, z = 51$): the bilateral precuneus, cuneus, superior parietal gyrus, superior occipital gyrus, and right angular gyrus; and (3) lower panel (ldACC-seeded cluster 2 with a cluster size of 69, $T = 5.60$, cluster-level familywise error rate [FWE]-corrected $P = 0.035$, peak MNI coordinates: $x = 24, y = 12, z = 57$): the right dorsolateral prefrontal cortex. Right: decreases in the AIC-seeded rsFC following AIC-TPS: (1) upper panel (rAIC-seeded cluster 1 with a cluster size of 143, $T = 6.74$, cluster-level FDR-corrected $P = 0.001$, peak MNI coordinates: $x = -18, y = 18, z = 18$; and rAIC-seeded cluster 2 with a cluster size of 109, $T = 6.18$, cluster-level FDR-corrected $P = 0.002$, peak MNI coordinates: $x = 24, y = 15, z = 3$): the left caudate and bilateral putamen; (2) middle panel (lAIC-seeded cluster 1 with a cluster size of 109, $T = 6.04$, cluster-level FDR-corrected $P = 0.002$, peak MNI coordinates: $x = 24, y = 15, z = 3$): the right putamen, caudate, and pallidum; and (3) lower panel (lAIC-seeded cluster 2 with a cluster size of 62, $T = 5.60$, cluster-level FDR-corrected $P = 0.027$, peak MNI coordinates: $x = 60, y = -39, z = 33$): the right supramarginal gyrus and superior temporal gyrus.

Supplementary Files

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