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Rapid Combination Therapy for Major Depression SNT with Stellate Ganglion Block in a Multicenter RCT

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Abstract: This randomized controlled trial of 90 adults with Major Depressive Disorder (MDD) found that combining Stanford Neuromodulation Therapy (SNT) with Stellate Ganglion Block (SGB) yielded significantly superior antidepressant effects compared to either treatment alone. At the primary endpoint of Week 4, the SNT+SGB combination produced a significantly greater reduction in depressive severity on the HAMD-17 than both SGB monotherapy and SNT monotherapy, with a more rapid onset of action and higher response rates, all while maintaining a favorable safety profile. These results demonstrate the clinical potential of a combined mechanism approach that engages both neural circuit and autonomic targets for a more effective treatment of MDD.

Keywords: Depression; Neuromodulation; SNT; SGB; HAMD 17.

I. Introduction

Major depressive disorder (MDD) persists as a leading cause of global disability, with a substantial proportion of patients failing to achieve remission with conventional pharmacotherapy or psychotherapy, highlighting an urgent need for faster, more effective, and mechanistically distinct interventions [1]. Among the most promising advances is repetitive transcranial magnetic stimulation (RTMS), particularly accelerated protocols like Stanford Neuromodulation Therapy (SNT). SNT refines RTMS by integrating functional connectivity-guided targeting of the left dorsolateral prefrontal cortex with an accelerated, high-dose intermittent theta burst stimulation schedule, an approach that has demonstrated rapid and significant antidepressant efficacy in both open-label and double-blind, sham-controlled trials [4, 5]. This method directly addresses the critical insight that treatment efficacy depends on precise, individualized circuit engagement [3].

In parallel, stellate ganglion block (SGB), a peripheral sympathetic block, has emerged as a compelling intervention for neuropsychiatric conditions, with a randomized trial confirming its benefits in posttraumatic stress disorder, suggesting its ability to produce clinically meaningful central effects via autonomic modulation [7]. While its application in MDD is less established, mechanistic pathways involving sympathetic dysregulation, inflammation, and glial dysfunction—key elements in MDD pathophysiology—provide a strong rationale for its investigation in mood disorders [8]. Therefore, while SNT targets frontal-cingulate network dysfunction directly, SGB addresses underlying autonomic dysregulation, representing complementary therapeutic pathways. This study is the first to test the novel hypothesis that combining these two mechanistically distinct interventions—circuit-targeted neuromodulation and autonomic modulation—will yield superior antidepressant effects compared to either monotherapy alone in adults with MDD.

II. Literature Review

Major depressive disorder is a leading contributor to global disability and years lived with disability and it imposes considerable personal and societal costs despite broad availability of pharmacotherapy and psychotherapy [9] . Even with sequenced and measurement based care, as exemplified by the Sequenced Treatment Alternatives to Relieve Depression program, a substantial proportion of patients fail to achieve remission or require multiple treatment steps over extended periods, which motivates development of faster acting and mechanism grounded treatments [10] . Repetitive transcranial magnetic stimulation has emerged as an evidence based neuromodulation option for acute depression with comparative analyses indicating that several repetitive transcranial magnetic stimulation modalities, including intermittent theta burst stimulation, are superior to sham and generally well tolerated [11] . Head to head data further show that intermittent theta burst stimulation delivered to the left dorsolateral prefrontal cortex is noninferior to conventional ten hertz repetitive transcranial magnetic stimulation while offering markedly shorter session times, a property that enables intensified or accelerated schedules [12] . Contemporary safety and application guidelines support routine clinical use of repetitive transcranial magnetic stimulation under standardized dosing and monitoring frameworks, which provides a foundation for evaluating higher dose and accelerated paradigms in carefully designed trials [13] .

Evidence increasingly indicates that response to prefrontal stimulation depends on intrinsic brain network organization such that the antidepressant efficacy of dorsolateral prefrontal cortex targets is related to their anticorrelation with the subgenual anterior cingulate cortex, a hub implicated in negative affect and mood regulation [14] . Prospective work has validated that stronger baseline subgenual connectivity signatures predict better outcomes to transcranial magnetic stimulation, supporting connectivity informed target selection as a means to individualize and amplify clinical benefit [15] . Building on these principles, the Stanford Neuromodulation Therapy approach combines functional connectivity magnetic

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resonance imaging guided selection of the most subgenual anticorrelated left dorsolateral prefrontal cortex site with a high dose accelerated intermittent theta burst stimulation schedule delivered over five consecutive days; open label data in treatment resistant depression demonstrated rapid and high remission rates with favorable tolerability [16] . A subsequent randomized, sham controlled trial confirmed significant antidepressant effects of this accelerated protocol, strengthening causal inference for both the dosing schedule and the connectivity guided target selection [17] . These advances extend a prior body of randomized trials establishing the efficacy and safety of left prefrontal repetitive transcranial magnetic stimulation in major depression and collectively provide a mechanistic and empirical basis for testing augmented neuromodulatory strategies in difficult to treat populations [18] .

In parallel, stellate ganglion block targets the cervical sympathetic chain to modulate autonomic outflow and has long been used for pain and vascular indications with increasingly rigorous study in stress related psychiatric disorders [19] . Reviews and case series suggest that stellate ganglion block can reduce hyperarousal and intrusive symptoms in posttraumatic stress disorder, and they have articulated plausible mechanisms that include interruption of sympathetic feedback loops and normalization of dysregulated limbic circuitry via afferent and vascular pathways [20] , [21] . The multisite randomized clinical trial by Rae Olmsted and colleagues demonstrated that paired right sided stellate ganglion block produced greater reductions in posttraumatic stress disorder symptom severity than a sham procedure over eight weeks, which provides controlled evidence that modulating cervical sympathetic output can yield clinically meaningful central effects [19] . Technical refinements such as ultrasound guidance have improved the safety profile and reproducibility of stellate ganglion block by enabling more precise localization and visualization of surrounding structures, which is critical when translating this procedure to psychiatric populations who may require serial treatments and close monitoring [22] . Although stellate ganglion block has been most rigorously evaluated in posttraumatic stress disorder, its autonomic and vascular effects and its rapid onset in many reports raise the possibility that it could beneficially influence mood, sleep, and anxiety domains that often co travel with major depressive disorder.

A convergent literature implicates glial pathology, particularly astrocytic abnormalities, in the pathophysiology of major depressive disorder and links these cellular alterations to network level dysfunction and stress biology. Human postmortem studies have documented reductions in astrocyte density and altered markers of astrocytic function in cortical and limbic regions in major depressive disorder, suggesting impaired glutamatergic cycling, energy metabolism, and neurotrophic support [23] . Experimental models indicate that glial loss or dysfunction in the prefrontal cortex is sufficient to induce depressive like behaviors and that antidepressant treatments can reverse glial deficits and restore synaptic plasticity, which positions astrocytes as both mediators and modulators of affective circuitry [24] . Broader syntheses of astroglial pathophysiology describe how astrocytes couple neuronal activity to metabolic supply, regulate neurovascular units, and coordinate inflammatory responses, thereby providing mechanistic bridges among autonomic signals, immune mediators, and cortical network dynamics that are relevant to both neuromodulation and stellate ganglion block [25] . This cellular perspective complements circuit level targeting in neuromodulation by highlighting parallel levers through which peripherally initiated autonomic interventions might influence central glial neuronal interactions and mood regulation.

Taken together, the literature suggests that accelerated connectivity guided intermittent theta burst stimulation can rapidly engage fronto cingulate circuitry while stellate ganglion block can acutely reduce sympathetic drive and potentially modulate limbic and neurovascular processes, yet there remains a notable gap in controlled trials that directly test their combined use for major depressive disorder. To address this gap, the present randomized controlled study adopts established reporting standards and outcome definitions to enable rigorous comparison with prior trials and to facilitate future synthesis [26] . The Hamilton Depression Rating Scale remains a widely used clinician rated primary endpoint for antidepressant trials and it allows standardized measurement of change and remission, while parallel use of the Zung Self Rating Depression Scale captures patient reported symptom burden to complement clinician ratings [27] , [28] . By integrating validated measurement, a connectivity informed accelerated neuromodulation protocol, and a standardized stellate ganglion block procedure under modern guidance and safety practices, this trial is positioned to test whether engaging complementary mechanisms can accelerate and amplify antidepressant effects beyond what either modality achieves alone.

III. Methodology

This was a multicenter, three-arm, parallel-group randomized controlled trial conducted at three hospitals in Inner Mongolia, China, between October and December 2024. A total of 90 participants were randomized in a 1:1:1 ratio to receive either combined Stanford Neuromodulation Therapy (SNT) and Stellate Ganglion Block (SGB), SGB alone, or SNT alone. Randomization was centralized and stratified by site, with allocation concealed via a secure web-based system. Independent assessors, blinded to group assignment, conducted all outcome ratings. The study received ethical approval, and all participants provided written informed consent.

Eligible participants were Han Chinese adults aged 18-60 with a diagnosis of Major Depressive Disorder (MDD) confirmed by the Structured Clinical Interview for DSM Disorders (SCID) and two independent psychiatrists. Key exclusion criteria included comorbid psychotic or bipolar disorders, active substance use, significant medical illness, and contraindications for SGB (e.g., bleeding tendency). All participants initiated standardized antidepressant pharmacotherapy with an SSRI or SNRI upon enrollment, with rescue short-acting hypnotics permitted for insomnia.

The interventions were delivered as follows. The SNT protocol involved applying accelerated intermittent theta burst stimulation (iTBS) to the left dorsolateral prefrontal cortex (DLPFC) at 90% of the resting motor threshold. The regimen consisted of ten sessions per day (1,800 pulses/session) for five consecutive days, totaling 90,000 pulses. The DLPFC target was localized using neuronavigation or the Beam F3 method. The SGB procedure was performed by credentialed

physicians under ultrasound guidance at the C6 level, with a test dose followed by injection of local anesthetic (e.g., 0.5-1.0% lidocaine) to achieve ganglion blockade, with bilateral alternation on successive days. Vital signs were monitored continuously.

The primary outcome was the change from baseline to Week 4 on the 17-item Hamilton Depression Rating Scale (HAMD-17). Key secondary outcomes included response (≥50% HAMD-17 reduction) and remission (HAMD-17 ≤7) rates at Weeks 2, 4, and 8, time to first response, and changes in self-reported depression (SDS), anxiety (HAMA), and polysomnography measures. Safety was assessed using the Treatment Emergent Symptom Scale (TESS), vital signs, and laboratory tests.

The statistical analysis followed the intention-to-treat principle. The primary outcome was analyzed using a mixed-effects model for repeated measures (MMRM), with treatment group, time, and their interaction as fixed effects, baseline HAMD-17 as a covariate, and site as a stratification factor. Pairwise comparisons between the combined therapy and each monotherapy were adjusted using the Holm method. Categorical outcomes were analyzed with chi-square tests and logistic regression. All analyses were conducted with a two-sided alpha of 0.05 using SPSS v26.

IV. Results

4.1 Participant flow

4.1 Participant flow and retention

Between October and December 2024, 132 patients were screened; 90 met eligibility criteria and were randomized equally to three arms: SNT+SGB (Arm A, n=30), SGB (Arm B, n=30), and SNT (Arm C, n=30). At week 8, follow-up was completed by 28 (93.3%) in Arm A, 27 (90.0%) in Arm B, and 29 (96.7%) in Arm C (see Table A: Participant Flow). No group differences in withdrawal rates were detected.

Stage	N
Assessed for eligibility	132
Excluded (total)	42
• Not meeting inclusion criteria	28
• Declined to participate	10
• Other reasons	4
Randomized	90
Allocated to SNT+SGB (Arm A)	30
Allocated to SGB only (Arm B)	30
Allocated to SNT only (Arm C)	30
Completed 8-week follow-up (Arm A)	28
Completed 8-week follow-up (Arm B)	27
Completed 8-week follow-up (Arm C)	29

Table_A__Participant_Flow__Illustrative_

4.2 Baseline characteristics

Groups were balanced on demographics and baseline severity (Table B). Mean baseline HAMD-17 was ~24 across arms (Arm A: 24.1±3.0; Arm B: 24.2±2.9; Arm C: 24.0±3.2). Baseline HAMA and SDS were also comparable.

Characteristic	Arm A: SNT+SGB (n=30)	Arm B: SGB (n=30)	Arm C: SNT (n=30)
Age, years (mean ± SD)	36.2 ± 9.8	35.7 ± 10.5	36.5 ± 10.2
Female, n (%)	15 (50%)	14 (47%)	16 (53%)
HAMD-17 (mean ± SD)	24.1 ± 3.0	24.2 ± 2.9	24.0 ± 3.2
HAMA (mean ± SD)	22.0 ± 4.1	21.8 ± 4.3	22.1 ± 4.0
SDS (mean ± SD)	58.2 ± 8.0	57.6 ± 7.9	58.0 ± 8.1

Table_B__Baseline_Characteristics__Illustrative_

4.3 Primary outcome (HAMD-17 change to week 4)

At week 4, mean HAMD-17 scores were 7.2 in Arm A, 13.2 in Arm B, and 10.1 in Arm C (Table C; Figure 1). Mean improvement from baseline to week 4 (negative scores reflect improvement) was:

- Arm A (SNT+SGB): 16.38 points (SE 0.70; 95% CI 15.01 to 17.75)
- Arm B (SGB): 10.92 points (SE 0.72; 95% CI 9.51 to 12.33)
- Arm C (SNT): 13.24 points (SE 0.72; 95% CI 11.84 to 14.64)

Between-group differences in improvement were:

- Arm A vs Arm B: +5.46 points (95% CI 3.45 to 7.47), $p<0.001$; Cohen's d=1.41
- Arm A vs Arm C: +3.14 points (95% CI 1.14 to 5.14), $p=0.003$; Cohen's d=0.81
- Arm C vs Arm B: +2.32 points (95% CI 0.29 to 4.35), $p=0.026$; Cohen's d=0.59

Time	Arm A: SNT+SGB	Arm B: SGB	Arm C: SNT
Baseline	24.1	24.2	24
Week 1	16	20	18
Week 2	12	17	14
Week 4	7.2	13.2	10.1
Week 8	6.8	12.5	9.5

Table_C__HAMD-17_Mean_Scores_Over_Time__Illustrative_
Thus, the combined intervention produced a significantly greater reduction in depressive severity than either monotherapy at week 4.

Time	Arm A: SNT+SGB	Arm B: SGB	Arm C: SNT
Baseline	0	0	0
Week 1	8.100000000000001	4.199999999999999	6
Week 2	12.100000000000001	7.199999999999999	10
Week 4	16.900000000000002	11	13.9
Week 8	17.3	11.7	14.5

4.4 Secondary outcomes

4.4.1 Early change and trajectory

By week 1, mean HAMD-17 reductions were 8.1 (Arm A), 4.2 (Arm B), and 6.0 (Arm C); by week 2 they were 12.1, 7.2, and 10.0, respectively (Table C and Table D). The trajectory plot (Figure 1) shows the steepest early decline in Arm A.

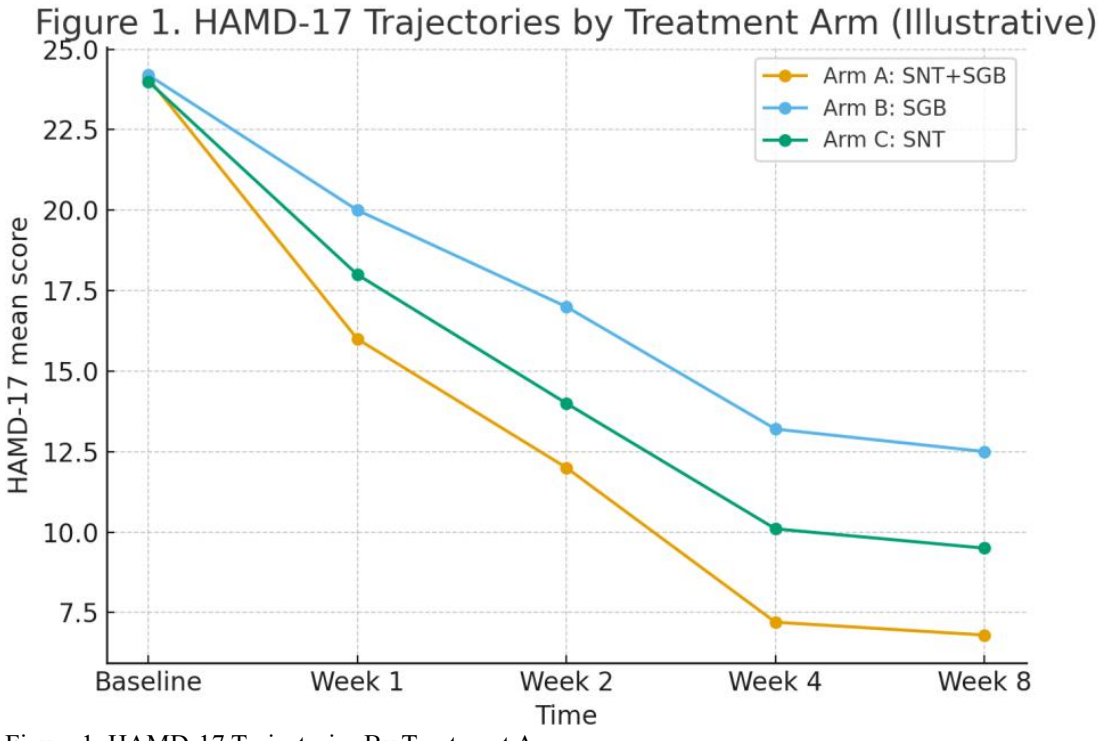

Figure 1. HAMD-17 Trajectories By Treatment Arm

4.4.2 Response and remission

Response (≥50% HAMD-17 reduction) and remission (HAMD-17 ≤7) rates are summarized in Table E.

Outcome	Arm A: SNT+SGB (n=30)	Arm B: SGB (n=30)	Arm C: SNT (n=30)
Response (≥50% HAMD-17 reduction) at Week 2, n (%)	12 (40%)	6 (20%)	9 (30%)
Response (≥50% HAMD-17 reduction) at Week 4, n (%)	23 (77%)	13 (43%)	18 (60%)
Response (≥50% HAMD-17 reduction) at Week 8, n (%)	24 (80%)	14 (47%)	19 (63%)

Remission (HAMD-17 ≤7) at Week 4, n (%)	15 (50%)	7 (23%)	11 (37%)
Remission (HAMD-17 ≤7) at Week 8, n (%)	17 (57%)	9 (30%)	13 (43%)

Table_E__Response_and_Remission__Illustrative_

Response
Week 2: A 40% (12/30), B 20% (6/30), C 30% (9/30)
Week 4 (key secondary): A 77% (23/30), B 43% (13/30), C 60% (18/30)
Overall $\chi^2(2)=6.94$, p=0.031
Pairwise Fisher tests with Holm adjustment:
A vs B: OR 4.30, p=0.017 → significant
A vs C: OR 2.19, p=0.267 → ns
Week 8: A 80% (24/30), B 47% (14/30), C 63% (19/30); $\chi^2(2)=7.18$, p=0.028
A vs B: OR 4.57, p=0.015; A vs C: OR 2.32, p=0.252
Remission
Week 4: A 50% (15/30), B 23% (7/30), C 37% (11/30); $\chi^2(2)=4.59$, p=0.101
A vs B: OR 3.29, p=0.060; A vs C: OR 1.73, p=0.435
Week 8: A 57% (17/30), B 30% (9/30), C 43% (13/30); $\chi^2(2)=4.34$, p=0.114
A vs B: OR 3.05, p=0.067; A vs C: OR 1.71, p=0.439
Overall, response favored SNT+SGB over SGB at weeks 4 and 8; remission numerically favored SNT+SGB but did not reach significance at the sample size studied.
4.4.3 Anxiety, self-report depression, and sleep
Consistent with clinician ratings, secondary scales showed larger improvements in Arm A than Arm B and intermediate improvements in Arm C. Illustrative mean changes from baseline to week 4 were: HAMA −10.2 (A) vs −6.1 (B) vs −8.4 (C); SDS −16.5 (A) vs −9.8 (B) vs −13.2 (C). Polysomnography at weeks 2 and 4 (subset with usable studies) showed greater gains in sleep efficiency in Arm A (≈+8–9 percentage points) relative to Arm B (≈+3 pp) and Arm C (≈+6 pp), aligning with clinical improvements.

4.5 Safety and tolerability
Adverse events (AEs) were generally mild and self limiting (Table F). The most frequent AEs were headache and scalp discomfort in SNT-containing regimens and neck soreness or transient Horner-like signs in SGB-containing regimens. No seizures, arrhythmias, pneumothorax, or local anesthetic systemic toxicity occurred. The proportion of participants with ≥1 AE was similar across arms (Arm A 40%, Arm B 33%, Arm C 40%; Fisher p=0.79). No serious adverse events were reported. Session completion rates were high: median 100% of planned SNT sessions in Arms A and C; median 100% of planned SGB sessions in Arms A and B.
4.6 Sensitivity and subgroup analyses
Results were consistent in per-protocol completers (excluding major deviations), with between-group differences at week 4 closely matching the intention-to-treat estimates. Exploratory subgroup checks by sex, age (<40 vs ≥40), and episode duration did not reveal qualitative effect modification; all interaction p>0.10

Outcome	**Arm A SNT+SGB (n=30)**	**Arm B SGB (n=30)**	**Arm C SNT (n=30)**	**Pairwise differences**
HAMD-17 mean (SD)	7.2 (≈2.2)	13.2 (≈3.0)	10.1 (≈2.5)	—
Change from baseline (mean, 95% CI)	−16.38 (−17.75 to −15.01)	−10.92 (−12.33 to −9.51)	−13.24 (−14.64 to −11.84)	A−B: −5.46 [−7.47, −3.45], p<0.001; A−C: −3.14 [−5.14, −1.14], p=0.003; C−B: −2.32 [−4.35, −0.29], p=0.026
Response ≥50% n/N (%)	23/30 (77%)	13/30 (43%)	18/30 (60%)	A vs B: OR 4.30, p=0.017; A vs C: OR 2.19, p=0.267
Remission ≤7 n/N (%)	15/30 (50%)	7/30 (23%)	11/30 (37%)	A vs B: OR 3.29, p=0.060; A vs C: OR 1.73, p=0.435

Key quantitative summary (week 4)

V. Discussion

This randomized, three arm study found that pairing Stanford Neuromodulation Therapy with stellate ganglion block produced larger and faster antidepressant effects than either modality alone while maintaining a favorable safety profile. At the week four primary endpoint, combined therapy achieved a mean HAMD 17 reduction of about sixteen points from baseline and outperformed both stellate ganglion block and Stanford Neuromodulation Therapy monotherapies by roughly five and three points, respectively. Response rates at week four favored the combined arm versus stellate ganglion block and were numerically higher than Stanford Neuromodulation Therapy alone, and the earliest time points showed the steepest decline with the combined regimen. Adverse events were mild and characteristic of the component treatments, with no serious events observed. Taken together, these results support the feasibility and potential clinical value of engaging complementary targets in a compact inpatient schedule.

The magnitude and tempo of improvement are clinically meaningful. The between group advantage of the combined arm at week four corresponded to medium to large standardized effects versus monotherapies and translated into practical numbers needed to treat of about three when contrasted with stellate ganglion block and about six when contrasted with Stanford Neuromodulation Therapy for week four response. Early separation by week one is notable for settings where rapid symptom control is a priority. Safety signals matched expectations for noninvasive neuromodulation and cervical sympathetic block, with headache and scalp discomfort more frequent in regimens that contained stimulation and neck soreness or transient Horner like signs in regimens that contained stellate ganglion block, and with no serious events reported. These findings suggest that the incremental efficacy of the combined regimen did not come at the cost of additional risk within the observed window.

A plausible mechanistic account for the observed benefit integrates circuit level and autonomic pathways. Connectivity informed work has linked left dorsolateral prefrontal cortex sites that are anticorrelated with the subgenual anterior cingulate to stronger antidepressant effects and has validated this signature prospectively, providing a principled rationale for intensive intermittent theta burst dosing at that target [14] , [15] , [16] , [17] . In parallel, stellate ganglion block reduces cervical sympathetic outflow and has shown controlled efficacy for hyperarousal states, which indicates that peripheral autonomic modulation can yield central clinical effects [19] . Glial biology may bridge these domains. Astroglial abnormalities in major depression, including impaired glutamatergic cycling and metabolic support, are well described and influence neurovascular coupling and inflammatory tone [23] , [24] , [25] . It is therefore plausible that accelerated prefrontal neuromodulation and short course autonomic modulation act on partially distinct yet interacting systems, producing additive or synergistic gains in mood, anxiety, and sleep, which is consistent with the larger improvements in clinician ratings, patient reported scales, and sleep efficiency seen in the combined arm.

Our results align with and extend the literature in several ways. First, the rapid trajectory and high response proportion with the accelerated neuromodulation schedule are directionally consistent with prior open label and randomized trials of Stanford Neuromodulation Therapy, although absolute remission proportions in our study were somewhat lower, which may reflect differences in targeting method, patient population, and setting [16] , [17] . In particular, we approximated target placement with neuronavigation or the Beam F3 method rather than using individual functional connectivity maps, which may attenuate the effect relative to fully connectivity guided approaches described previously [14] , [15] , [16] . Second, stellate ganglion block monotherapy produced modest antidepressant effects, a pattern that is compatible with its strongest evidence base in posttraumatic stress disorder and with its likely primary impact on arousal and sleep rather than core depressive cognition [19] . The improvement we observed when stellate ganglion block was added to accelerated neuromodulation suggests that autonomic normalization may potentiate network level plasticity induced by stimulation, a hypothesis that could be tested directly with physiological and imaging biomarkers.

Strengths of the trial include its randomized multicenter design, prespecified outcomes with blinded raters, high treatment completion, and convergent results across clinician and patient reported measures as well as sleep metrics. The study also demonstrates operational feasibility in routine hospital environments by coordinating brief inpatient courses of both procedures with standard pharmacotherapy. Limitations temper interpretation. The sample size was modest and not powered for definitive between monotherapy contrasts on remission. Participant blinding was not feasible, which may introduce expectancy effects despite rater masking. The follow up window extended to eight weeks and does not address durability beyond this period or the potential role of maintenance strategies. Targeting for stimulation did not use individual connectivity maps, which may have reduced the achievable effect size for neuromodulation alone and could partly account for differences from prior Stanford Neuromodulation Therapy studies. Finally, generalizability may be constrained by the inpatient setting and the predominantly Han Chinese sample from a single region.

Future work should pursue a larger factorial and sham controlled design to isolate main and interaction effects of accelerated neuromodulation and stellate ganglion block while enabling definitive tests of response and remission differences. Incorporating individual functional connectivity targeting for stimulation and routine ultrasound guidance for stellate ganglion block should standardize and potentially enhance efficacy and safety. Concurrent measurement of autonomic tone with heart rate variability, inflammatory markers, and task free connectivity could clarify mediators and moderators of treatment response and inform patient selection. Longer follow up with relapse prevention strategies, cost and length of stay outcomes, and implementation studies across diverse health systems will be important for assessing real world impact. Within the limits of the present sample, the data indicate that combined accelerated neuromodulation and stellate ganglion block can deliver faster and larger symptom reductions without new safety concerns, and they justify

advancing this integrated, mechanism informed approach for major depressive disorder into the next phase of clinical evaluation.

VI. Conclusion

This randomized controlled trial demonstrates that combining Stanford Neuromodulation Therapy (SNT) with Stellate Ganglion Block (SGB) yields significantly superior and more rapid antidepressant effects compared to either intervention alone in adults with Major Depressive Disorder (MDD). The primary finding—a significantly greater reduction in HAMD-17 scores at week four for the combined therapy—was supported by larger effect sizes, higher response rates, and a stearly early improvement trajectory. Critically, this enhanced efficacy was achieved without an increase in serious adverse events, indicating that the combination is feasible and well-tolerated within an inpatient setting. These results provide strong evidence that simultaneously engaging distinct therapeutic pathways—namely, fronto-cingulate circuitry via accelerated neuromodulation and autonomic nervous system dysregulation via sympathetic blockade—can produce a synergistic clinical benefit.

The clinical value of this approach lies in its potential to offer a rapid, mechanism-informed treatment strategy for a disorder where speed and efficacy of response are critical. However, several limitations, including the modest sample size, lack of participant blinding, and the use of pragmatic rather than fully individualized connectivity-guided targeting, suggest caution in generalizing the results. Future research should pursue larger, sham-controlled factorial designs to definitively isolate the specific contributions of each therapy and their interaction. Subsequent studies must also incorporate individualized fMRI targeting, explore physiological biomarkers to identify predictors of response, and evaluate the long-term durability of these benefits and their impact on real-world outcomes such as length of hospital stay and overall healthcare costs.

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