Pacific International Journal, Vol. 9(4); 2026
ISSN (Print) 2663-8991, ISSN (Online) 2616-4825[1]
DOI: 10.55014/pij.v9i4.973
https://rclss.com/index.php/pij

Synergistic Neuromodulation and Stellate Ganglion Block in Depression: A Neuroimmune Framework

Eugene Lipov[1], Siddharth Nair[2], Ahmed Nosir[3]

[1]Stella Mental Health Center, Westmont, 60559, United States of America ;
[2]Midwestern University, Downers Grove, 60515, United States of America ;
[3]College of Medicine, Tanta University, Tanta 31511, Al Gharbīyah, Egypt ;
Email: elipovmd@aol.com

Abstract:Background: Major depressive disorder (MDD) is a leading cause of global disability, with many patients remaining resistant to standard pharmacologic and psychotherapeutic treatments. Increasing evidence implicates dysfunctional neural circuitry, autonomic imbalance, and neuroimmune dysregulation in the pathophysiology of MDD. A novel therapeutic strategy combining Stanford Neuromodulation Therapy (SNT) with stellate ganglion block (SGB) may target these interacting systems and potentially improve treatment outcomes in patients with MDD.
Objective:This commentary aims to review the available clinical evidence and mechanistic rationale for combining SNT with SGB in the treatment of major depressive disorder (MDD), a combination that may produce synergistic therapeutic effects.**Results**: The combination of SNT + SGB was associated with more rapid and greater symptom reduction compared with either monotherapy, with favorable tolerability reported across two clinical studies. Mechanistically, SNT engages fronto-cingulate circuitry, modulates glial–immune signaling, and enhances parasympathetic tone. In contrast, SGB reduces sympathetic outflow and attenuates pro-inflammatory mediators, including IL-6. These complementary effects likely converge on shared neuroimmune pathways, producing synergistic antidepressant outcomes.**Conclusion**: Integrating cortical neuromodulation with autonomic regulation represents a coherent neuroimmune strategy for treatment-resistant MDD. Combined SNT + SGB may enhance antidepressant efficacy and durability, warranting validation in larger biomarker-informed trials.
Keywords: Stellate ganglion block, Stanford Neuromodulation Therapy, Treatment-resistant depression, Autonomic regulation, Neuroimmune

1. Introduction

1.1 Overview

Major depressive disorder (MDD) is one of the most prevalent and disabling neuropsychiatric disorders worldwide, affecting more than 280 million individuals. Despite widespread use of antidepressant medications and psychotherapy, many patients fail to achieve sustained remission, highlighting the burden of treatment-resistant depression and limitations of conventional therapies [1].

Current models conceptualize MDD as a disorder of dysfunctional neural networks, particularly fronto-cingulate circuits that regulate mood, cognition, and emotional processing. These abnormalities are frequently accompanied by systemic dysregulation, including autonomic imbalance and chronic low-grade inflammation, which may contribute to symptom persistence and clinical heterogeneity [2]. Neuroinflammation appears to play a key role in MDD pathophysiology, characterized by microglial activation and elevated pro-inflammatory cytokines, particularly interleukin-6 (IL-6) [3]. Interventions capable of modulating neural circuits, autonomic balance, and neuroimmune signaling may therefore offer advantages in refractory depression. Both Stanford Neuromodulation Therapy (SNT) and stellate ganglion block (SGB) have independently demonstrated antidepressant effects.

1.2 Stanford Neuromodulation Therapy (SNT)

A major recent advance in depression treatment is transcranial magnetic stimulation (TMS), particularly Stanford Neuromodulation Therapy (SNT), an accelerated protocol using functional connectivity–guided targeting of the left dorsolateral prefrontal cortex (DLPFC). Individualized targeting enhances modulation of fronto-cingulate networks, especially the subgenual anterior cingulate cortex (sgACC), a key region implicated in mood regulation and treatment resistance [4].

In addition to circuit modulation, TMS influences autonomic function, including heart-rate deceleration consistent with increased parasympathetic tone. Emerging evidence also suggests immunomodulatory effects, with reductions in pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, linking cortical neuromodulation to downstream neuroimmune regulation in depression [5].

[1][Received 10 June 2026; Accepted 11 August 2026; Published (online) 20, August, 2026]

1.3 Stellate Ganglion Block (SGB)

Stellate ganglion block is a peripheral sympathetic intervention that transiently inhibits cervical sympathetic outflow. By reducing sympathetic overactivity, SGB can alleviate hyperarousal and anxiety symptoms commonly seen in post-traumatic stress disorder (PTSD), a condition frequently comorbid with treatment-resistant depression [6].

Beyond symptomatic improvement, SGB may influence neuroinflammatory signaling through central autonomic pathways regulating stress-related immune responses. Preclinical and clinical studies suggest sympathetic blockade reduces circulating pro-inflammatory cytokines, including IL-6 and TNF-α, thereby affecting cytokine-mediated depressive mechanisms [7]. As a relatively safe and minimally invasive procedure, SGB represents a promising adjunctive therapy within multidimensional treatment models for MDD and PTSD [8].

Within this framework, neuromodulatory interventions targeting both neural circuitry and autonomic regulation have gained increasing attention. SNT and SGB represent complementary approaches acting on distinct yet convergent biological pathways that may produce synergistic clinical effects [9]. The objective of this report is to summarize available clinical evidence supporting this combined approach and to explore potential mechanisms underlying the observed therapeutic benefits.

2. Evidence from Clinical Studies

2.1 Multicenter Randomized Controlled Trial

The primary clinical evidence for combined SNT + SGB derives from a multicenter randomized controlled trial conducted by Wu et al. [9]. Ninety adults with MDD were randomized to SNT + SGB, SGB monotherapy, or SNT monotherapy.

The SNT protocol used accelerated intermittent theta-burst stimulation (10 sessions/day for 5 days; 90,000 total pulses). SGB was performed under ultrasound guidance at the C6 level, with alternating laterality.

At Week 4, the combination group showed significantly greater HAMD-17 score reduction than either monotherapy. Response rates were 77% for SNT + SGB, 60% for SNT, and 43% for SGB. Improvements emerged rapidly, with the steepest decline in the combination group evident by Week 1. Group differences in response rates remained significant at Weeks 4 and 8. All interventions were well tolerated, with no serious adverse events[9]..

2.2 Case Evidence

A representative clinical case reported by Leapo et al. [10] involved a 54-year-old veteran with comorbid MDD and PTSD. After partial PTSD improvement with repeated SGB, depressive symptoms remained severe (PHQ-9 = 25). Following initiation of left-DLPFC rTMS alongside continued SGB, the patient's PHQ-9 decreased to 8, indicating marked clinical improvement. Both patient and spouse described a clear synergistic benefit, with no adverse autonomic effects observed [10].

Discussion

Major depressive disorder (MDD) is increasingly conceptualized as a neuroimmune condition characterized by chronic low-grade inflammation, glial dysfunction, and dysregulated cytokine signaling. Converging evidence demonstrates elevated peripheral and central levels of pro-inflammatory cytokines—including interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β)—in individuals with MDD. These immune alterations disrupt monoaminergic neurotransmission, impair synaptic plasticity, and promote microglial activation, thereby contributing to depressive symptomatology [11,12]. Clinically, increased inflammatory signaling has been associated with greater symptom severity, reduced treatment responsiveness, and more refractory disease phenotypes.

Among these mediators, IL-6 plays a particularly central mechanistic role. Elevated IL-6 levels correlate with depression severity, cognitive dysfunction, and diminished response to antidepressant therapy. IL-6 influences the central nervous system either by crossing the blood–brain barrier or through endothelial and vagal signaling pathways. Within the brain, it promotes microglial activation, suppresses hippocampal neurogenesis, and disrupts synaptic plasticity in prefrontal–limbic circuits involved in mood regulation [12].

IL-6 also induces indoleamine-2,3-dioxygenase (IDO) activity, shifting tryptophan metabolism toward the kynurenine pathway. This reduces serotonin availability while generating neuroactive metabolites such as quinolinic acid that enhance glutamatergic excitotoxicity and destabilize cortical networks [13]. Together, these mechanisms position IL-6 as a key inflammatory mediator and a biologically plausible therapeutic target in treatment-resistant and inflammation-associated MDD.

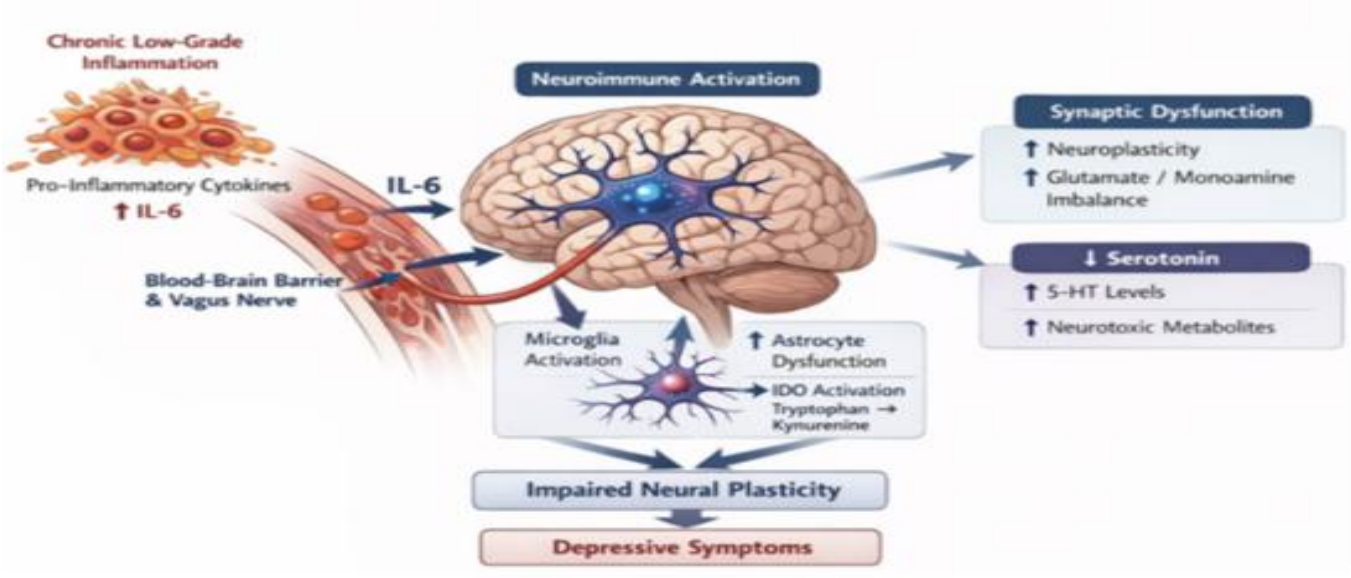

Figure 1. Neuroimmune model of major depressive disorder (MDD).
Major depressive disorder is associated with chronic low-grade inflammation, with interleukin-6 (IL-6) serving as a key upstream mediator linking peripheral immune activation to central nervous system (CNS) dysfunction. IL-6 accesses the brain through blood–brain barrier (BBB), endothelial, and vagal pathways, promoting glial activation and disruption of immune–neural homeostasis. Microglial activation and astrocyte dysfunction impair synaptic plasticity and neurotransmission, while IL-6–induced indoleamine-2,3-dioxygenase (IDO) activation shifts tryptophan metabolism toward the kynurenine pathway, reducing serotonin availability and generating neurotoxic metabolites. These processes converge to reduce neural plasticity and contribute to depressive symptoms.
Abbreviations: MDD, major depressive disorder; IL-6, interleukin-6; CNS, central nervous system; BBB, blood–brain barrier; IDO, indoleamine-2,3-dioxygenase.

Depression has also been associated with systemic physiological effects, including reduced bone mass and increased risk of osteoporotic fractures. Experimental studies suggest that stress-induced sympathetic activation may contribute to this relationship. In rodent models, chronic mild stress (CMS) produces behavioral depression accompanied by reduced trabecular bone volume, number, and connectivity in femoral and vertebral bone. These changes reflect impaired bone formation [14] .
Antidepressant therapy that prevents the behavioral effects of CMS also prevents the reduction in bone formation and significantly attenuates bone loss. CMS-induced skeletal deterioration is associated with elevated bone norepinephrine levels and can be blocked by β-adrenergic antagonism with propranolol, indicating sympathetic mediation. These findings highlight an integrated interaction among behavioral stress responses, central neural regulation, and skeletal metabolism. Given the frequent coexistence of depression and osteoporosis in aging populations, depression may represent an important risk factor for bone loss and fracture vulnerability[14].
Mechanistic Synergy
The combination of cortical neuromodulation with peripheral sympathetic blockade represents a mechanistically coherent strategy for MDD. SNT enhances parasympathetic tone and normalizes dysfunctional fronto-cingulate circuitry [15], while SGB suppresses excessive sympathetic outflow and associated inflammatory signaling. Most clinical SGB protocols employ right-sided blockade, consistent with evidence for right-hemisphere sympathetic predominance [16].

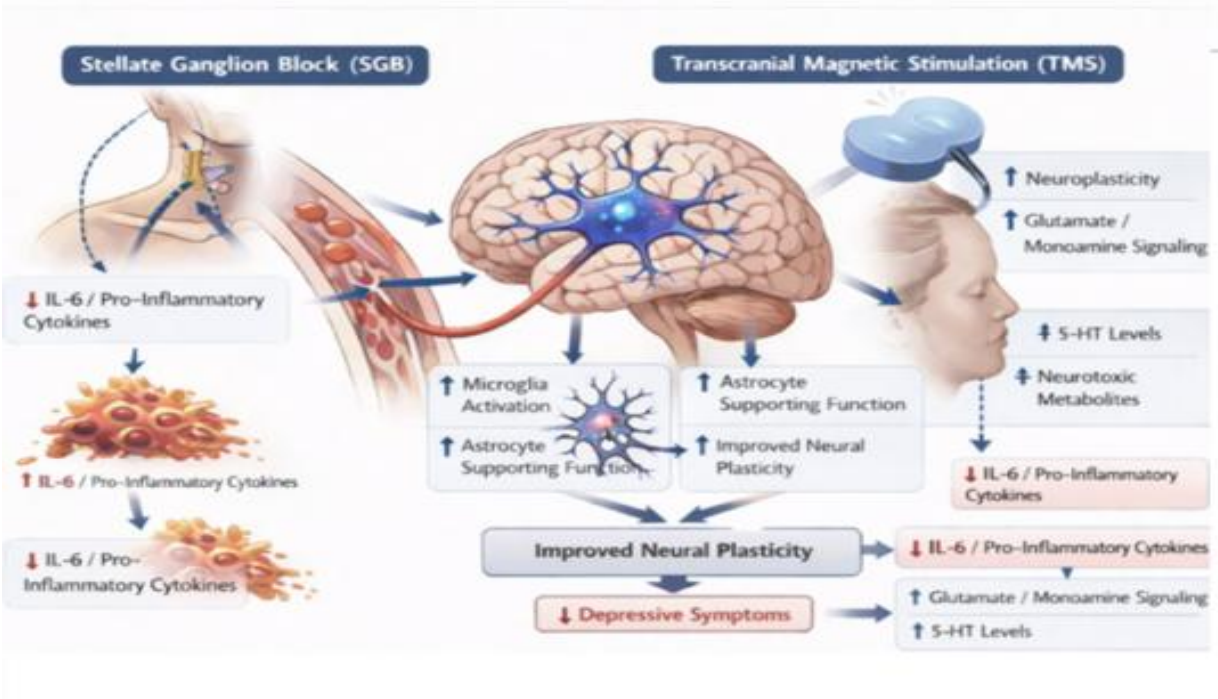

Figure 2. Effects of stellate ganglion block and transcranial magnetic stimulation on neuroimmune dysfunction in major depressive disorder.
Stellate ganglion block (SGB) reduces sympathetic outflow and pro-inflammatory cytokine signaling, particularly interleukin-6 (IL-6), while transcranial magnetic stimulation (TMS) enhances fronto-cortical plasticity, monoaminergic and glutamatergic signaling, and glial support, together converging on improved neural plasticity and reduced depressive symptoms.
Abbreviations: SGB, stellate ganglion block; TMS, transcranial magnetic stimulation; IL-6, interleukin-6; 5-HT, serotonin.

Within this framework, reduction of right-sided sympathetic tone combined with enhancement of left-sided cortical parasympathetic modulation may yield additive or synergistic effects, particularly in patients with comorbid MDD and PTSD. Together, these interventions may converge on immunomodulatory pathways, reducing IL-6 and TNF-α, accelerating symptom improvement, and enhancing treatment tolerability [9,10]. Nonetheless, precise interactions between cortical neuromodulation, sympathetic inhibition, and synaptic plasticity remain incompletely understood, underscoring the need for biomarker-driven mechanistic investigation.

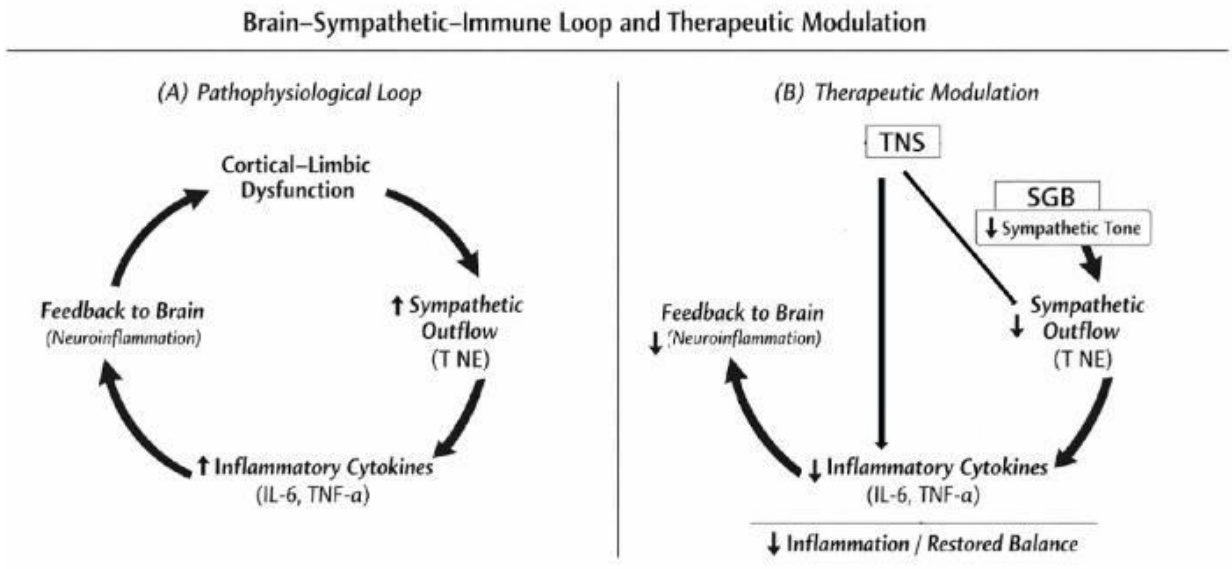

Figure 3 . Brain–Sympathetic–Immune Loop in Depression
Left: Increased immune activation and sympathetic nervous system (SNS) activity interact bidirectionally, contributing to depression.

Right: Stellate ganglion block (SGB) reduces sympathetic activity and inflammation, while transcutaneous neuromodulation stimulation (TNS) enhances parasympathetic activity and modulates immune activation. Together, these interventions restore autonomic and immune balance, reducing depressive symptoms.

4. Limitations of Current Evidence

Despite promising early findings, several limitations constrain interpretation:

1. **Lack of individualized connectivity-guided targeting** in the RCT may have attenuated SNT efficacy relative to fully personalized protocols.
2. **Absence of sham-controlled blinding** introduces potential expectancy effects.
3. **Limited long-term follow-up** prevents assessment of durability and maintenance strategies.
4. **Insufficient power for remission contrasts** limits definitive remission comparisons.

5. Future Research Directions

Future studies should prioritize factorial sham-controlled randomized trials to disentangle additive versus synergistic effects. Biomarker-driven investigations incorporating inflammatory cytokines (IL-6, TNF-α), heart-rate variability, and functional connectivity imaging are warranted. Longitudinal neuroimaging may elucidate plasticity mechanisms underlying sustained improvement. Individualized connectivity-guided SNT targeting may further optimize therapeutic precision [17].

6. Additional Considerations

Mechanistic interactions between cortical neuromodulation and peripheral sympathetic blockade remain incompletely characterized. The combined intervention is resource-intensive, potentially limiting scalability. Variability in SGB technique and laterality introduces heterogeneity. Long-term safety and cost-effectiveness data are needed to guide implementation .

7. Conclusion

Major depressive disorder is increasingly understood as a disorder of dysregulated neural circuitry, autonomic imbalance, and neuroimmune dysfunction. In this context, the combination of Stanford Neuromodulation Therapy and stellate ganglion block represents a rational, multimodal intervention simultaneously targeting cortical network dysfunction, sympathetic overactivity, and inflammation-driven pathophysiology.

Evidence from a multicenter randomized trial and convergent case data suggests that combined SNT + SGB produces more rapid symptom reduction, higher response rates, and favorable tolerability compared with either modality alone. Dual modulation of fronto-cingulate circuitry and the autonomic-immune axis—particularly attenuation of IL-6 signaling—offers a compelling mechanistic framework.

While limitations remain, these findings establish a foundation for future biomarker-guided, sham-controlled trials. Collectively, current evidence positions combined neuromodulatory and autonomic interventions as a promising next step in precision, mechanism-based treatment for treatment-resistant depression.

References :

[1] World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: WHO; 2017.

[2] Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct 2008; 213: 93-118 [PMID: 18704495 DOI: 10.1007/s00429-008-0189-x]

[3] Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016; 16: 22-34 [PMID: 26711676 DOI: 10.1038/nri.2015.5]

[4] Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 2012; 72: 595-603 [PMID: 22658708 DOI: 10.1016/j.biopsych.2012.04.028]

[5] Liu S, Wang X, Yu R, Sun Y. Effect of transcranial magnetic stimulation on treatment effect and immune function. Saudi J Biol Sci 2022; 29: 379-384 [PMID: 35002433 DOI: 10.1016/j.sjbs.2021.08.104]

[6] Lipov EG, Joshi JR, Sanders S, Slavin KV. A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD). Med Hypotheses 2009; 72: 657-661 [PMID: 19237252 DOI: 10.1016/j.mehy.2009.01.009]

[7] Lipov 2020 immune

[8] Sussman D, Tassone VK, Gholamali Nezhad F, Wu M, Adamsahib F, Mattina GF, Pazmino-Canizares J, Demchenko I, Jung H, Lou W, Ladha KS, Bhat V. Local Injection for Treating Mood Disorders (LIFT-MOOD): A Pilot Feasibility RCT of Stellate Ganglion Block for Treatment-Resistant Depression. Chronic Stress (Thousand Oaks) 2023; 7: 24705470231160315 [PMID: 36895443 DOI: 10.1177/24705470231160315]

[9] Wu P. Rapid Combination Therapy for Major Depression SNT with Stellate Ganglion Block in a Multicenter RCT. PIJ 2025; 8: 15-22 [DOI: 10.55014/pij.v8i6.917]

[10] Leapo L, Polick S, Fryml L. Repetitive Transcranial Magnetic Stimulation in Patient Receiving Stellate Ganglion Blocks for PTSD. J ECT 2025; 41: e25-e26 [PMID: 40423508 DOI: 10.1097/YCT.0000000000001099]

[11] Hassamal S. Chronic stress, neuroinflammation, and depression: an overview of pathophysiological mechanisms and emerging anti-inflammatories. Front Psychiatry 2023; 14: 1130989 [PMID: 37252156 DOI: 10.3389/fpsyt.2023.1130989]

[12] Roohi E, Jaafari N, Hashemian F. On inflammatory hypothesis of depression: what is the role of IL-6 in the middle of the chaos? J Neuroinflammation 2021; 18: 45 [PMID: 33593388 DOI: 10.1186/s12974-021-02100-7]
[13] Myint AM, Schwarz MJ, Müller N. The role of the kynurenine metabolism in major depression. J Neural Transm (Vienna) 2012; 119: 245-251 [PMID: 22139324 DOI: 10.1007/s00702-011-0741-3]
[14] Yirmiya R, Goshen I, Bajayo A, Kreisel T, Feldman S, Tam J, Trembovler V, Csernus V, Shohami E, Bab I. Depression induces bone loss through stimulation of the sympathetic nervous system. Proceedings of the National Academy of Sciences. 2006 Nov 7;103(45):16876-81.
[15] Cole EJ, Stimpson KH, Bentzley BS, Gulser M, Cherian K, Tischler C, Nejad R, Pankow H, Choi E, Aaron H, Espil FM, Pannu J, Xiao X, Duvio D, Solvason HB, Hawkins J, Guerra A, Jo B, Raj KS, Phillips AL, Barmak F, Bishop JH, Coetzee JP, DeBattista C, Keller J, Schatzberg AF, Sudheimer KD, Williams NR. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. Am J Psychiatry 2020; 177: 716-726 [PMID: 32252538 DOI: 10.1176/appi.ajp.2019.19070720]
[16] Alkire MT, Hollifield M, Khoshsar R, Nguyen L, Alley SR, Reist C. Neuroimaging suggests that stellate ganglion block improves post-traumatic stress disorder (PTSD) through an amygdala mediated mechanism. In The Anesthesiology Annual Meeting 2015 Oct 24.

Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, Fetcho RN, Zebley B, Oathes DJ, Etkin A, Schatzberg AF, Sudheimer K, Keller J, Mayberg HS, Gunning FM, Alexopoulos GS, Fox MD, Pascual-Leone A, Voss HU, Casey BJ, Dubin MJ, Liston C. Erratum: Resting-state connectivity biomarkers define neurophysiological subtypes of depression. Nat Med 2017; 23: 264 [PMID: 28170383 DOI: 10.1038/nm0217-264d]