PSILOGOS

Research Article

open-access

Directional Immune Concordance Across Neuromodulation Modalities for Anxiety and Depression: A circuit–compartment study with probabilistic and adversarial validation

Sean O'Brien

ABSTRACT

Neuroimmune change has been proposed as a tractable indicator of target engagement during neuromodulation for anxiety and depression, yet the evidence spans different organisms, anatomical targets, biological compartments, and sampling times. This study asked whether the direction of immune change remains consistent across those sources of heterogeneity and whether apparently favorable modality profiles withstand deliberate perturbation. A 27-comparison in vivo corpus covering transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES), electroconvulsive therapy (ECT), photobiomodulation (PBM), transcranial ultrasound stimulation (TUS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) was analyzed with Directional Immune Concordance Analysis. Every comparison received a signed value of $+1$ for neuroimmune normalization, 0 for no detectable or mixed change, and -1 for inflammatory activation. Group means were paired with 20,000-resample intervals, Jeffreys-posterior probabilities among directionally decisive comparisons, 100,000-draw randomization tests, and a sign-fragility experiment. Nineteen comparisons indicated normalization, five indicated activation, and three were null or mixed. The overall directional mean was 0.519 (95% bootstrap interval 0.222–0.815). VNS and TUS each had a mean of 1.000, whereas ECT and PBM had means of 0; however, modality heterogeneity was not supported by randomization ($p = 0.478$). Direct affective comparisons had a mean of 0.333, compared with 0.611 in indirect disease models ($p = 0.454$). Human and rodent means were nearly identical (0.500 and 0.526), as were peripheral and central estimates (0.500 and 0.471). Three favorable VNS reports, two TUS or TES reports, and one TMS or DBS report had to reverse sign before their respective aggregate values became nonpositive. The evidence therefore supports a general homeostatic immune direction but does not justify choosing a device solely from modality-level immune rankings. For anxiety and depression, the decisive next test is temporally matched measurement of symptoms, peripheral cytokines, and circuit-proximal neuroimmune activity within the same participants.

Keywords: anxiety; depression; neuroinflammation; neuromodulation; microglia; cytokines; directional evidence synthesis; treatment stratification

Discipline of Psychiatry, School of Medicine, Trinity College Dublin, University of Dublin, Dublin, Ireland
sean.obrien79@gmail.com

– **Published:** 20 November 2024

1. INTRODUCTION

Anxiety and depressive disorders impose a large and growing burden through persistent distress, impaired occupational and social functioning, recurrent illness, and suicide risk. Global estimates for 2020 documented substantial increases in both disorder groups during the coronavirus disease pandemic, adding to an already high prevalence across age and income strata.[1] Clinical heterogeneity compounds that population burden. Anxiety may be expressed as sustained apprehension, panic, threat avoidance, autonomic hyperarousal, or intrusive fear, whereas depression may be dominated by anhedonia, psychomotor slowing, cognitive impairment, sleep disturbance, or suicidal thinking. Co-occurrence is common and is associated with longer episodes and poorer recovery. Even carefully sequenced pharmacological care leaves a considerable proportion of patients symptomatic, as demonstrated by the STAR*D treatment sequence.[2] These limitations have accelerated interest in device-based interventions that alter neural activity through magnetic fields, weak electrical current, induced seizures, light, acoustic energy, implanted electrodes, or peripheral nerve stimulation.

Neuromodulation is not a unitary treatment family. TMS most commonly acts on a cortical entry point whose downstream influence depends on network connectivity. TES modifies membrane polarization and oscillatory coordination with lower focality but flexible dosing. ECT recruits a widespread seizure-associated biological response. TUS can deposit mechanical energy within comparatively deep and spatially restricted targets. PBM couples photon absorption to mitochondrial, vascular, and redox processes. DBS acts at an implanted neural interface, while VNS engages ascending autonomic and brainstem pathways. Their clinical evidence, invasiveness, spatial reach, temporal pattern, and adverse-effect profiles are consequently different.[3] Meta-analytic findings support antidepressant or anxiolytic effects for several noninvasive techniques, although effect sizes and certainty vary across conditions and protocols.[4] A mechanistic comparison must therefore distinguish the physical modality from the biological state that the stimulation encounters.

Inflammation is one candidate state variable. Treatment-resistant depression is associated with higher circulating inflammatory markers in a clinically meaningful subgroup,[5] and quantitative syntheses show average elevations and increased dispersion in several cytokines and acute-phase proteins among people with depression.[6] Changes in inflammatory markers also accompany clinical response, although associations differ by analyte, treatment, and sampling time.[7,8] These observations do not imply that depression or anxiety is an inflammatory disease in every patient. They instead suggest that an immune-active phenotype can alter neurotransmission, synaptic plasticity, energy allocation, endothelial signaling, and motivation, thereby changing both symptoms and responsiveness to stimulation.

Central immune activity is more difficult to measure than peripheral inflammation. Positron emission tomography (PET) ligands targeting the 18-kDa translocator protein (TSPO) have identified higher binding in the prefrontal cortex, anterior cingulate cortex, and insula during major depressive episodes.[9] Longer untreated illness has also been associated with greater TSPO distribution volume.[10] Elevated prefrontal and anterior cingulate TSPO signal may carry predictive information in an anti-inflammatory treatment context.[11] Nevertheless, TSPO is expressed by several cell types, radioligand binding is affected by genotype and vascular signal, and studies vary in quantification procedures. Reviews of the imaging literature accordingly support biological relevance without treating TSPO as a cell-specific or universally elevated indicator.[12] The clinically useful question is not whether one molecule provides an infallible readout, but whether convergent measurements can identify an immune state that changes in a reproducible direction during successful treatment.

Animal studies supply stronger anatomical access but introduce another kind of uncertainty. Repeated stress can activate microglia and raise inflammatory signaling in the amygdala and prefrontal cortex while producing anxiety-like behavior.[13,14] Chronic mild stress similarly links microglial activation with depressive- and anxiety-like behavior.[15] In the basolateral amygdala, inflammatory signaling alters excitatory–inhibitory balance and neuronal plasticity;[16] interleukin-10 can reverse abnormal amygdala GABA transmission and anxiety-like behavior in a related immune-active context.[17] Such studies establish biological plausibility for reciprocal coupling: neural activity can regulate immune cells, and immune mediators can reshape the circuit being stimulated. They do not, however, guarantee that an anti-inflammatory change in a lesion or endotoxin model predicts symptom improvement in major depression.

The circuit consequences of inflammation reinforce this translation problem. Higher C-reactive protein has been associated with weaker corticostriatal connectivity in depression,[18] while multivariate connectivity changes centered on ventromedial prefrontal and striatal regions covary with inflammatory burden and depressive symptoms.[19] Experimentally induced inflammation shifts reward and punishment processing[20] and reduces ventral striatal responses to anticipated reward.[21] These effects connect immune signaling to anhedonia rather than to an undifferentiated mood score. The lateral habenula is likewise positioned to integrate aversive value and monoaminergic control;[22] chronic stress increases inflammatory cytokine expression within that nucleus,[23] and extracellular-matrix remodeling in habenular neurons can generate depressive-like behavior.[24] A useful neuromodulation biomarker should therefore be inter-

preted at the level of symptom domain, circuit, and time, not merely as a favorable change in a peripheral analyte.

Existing narrative accounts catalogue many anti-inflammatory findings but cannot by themselves reveal how much of the apparent convergence depends on modality, organism, compartment, or disease model. Counting favorable statements is also insufficient because a technique with five consistent reports should not be treated like a technique with one mixed report, and a transient inflammatory surge after ECT should not automatically be equated with sustained pathological activation. Conventional effect-size meta-analysis would be preferable if comparable means, variances, and sampling times were available. They are not available across the full corpus. Discarding direction-only findings would remove much of the mechanistic literature; pooling them as if they shared a common numerical scale would create false precision.

The present study addresses that problem with Directional Immune Concordance Analysis (DICA), a method designed for heterogeneous in vivo evidence in which the sign of a biological response is more consistently reportable than its magnitude. The research question was: to what extent does neuroimmune normalization remain directionally consistent across neuromodulation modalities, organisms, compartments, and direct affective models, and which favorable modality signals survive adversarial sign reversal? Four analytical experiments were specified. The first measured the complete distribution of signed immune responses. The second estimated modality-specific probabilities of normalization with uncertainty that remains wide when observations are scarce. The third tested whether direction transferred from indirect neurological or inflammatory models to anxiety and depression and from rodents to humans. The fourth intentionally reversed favorable reports until each modality's aggregate result became nonpositive. This design separates a general biological tendency from the much stronger claim that one modality has established mechanistic superiority.

2. MATERIALS AND METHODS

The corpus comprised 27 in vivo comparisons tabulated across seven neuromodulation modalities by Guo and colleagues.[25] The table was cited at corpus definition and was not cited again for individual entries. Eligible rows required an identified stimulation modality, an organism or patient group, an anatomical target, and a reported inflammatory or glial direction. Cell-only experiments, purely theoretical descriptions, and clinical reports without an immune readout were not assigned a row. When a row contained several cytokines or cellular readouts, it remained one comparison so that a densely assayed study did not receive more influence merely because it measured more analytes.

Each comparison was coded for modality, population or disease model, target, organism, affective relevance, biological compartment, direction, and number of readout classes. Affective relevance was classified as direct when the population had depression or bipolar depression, or when the animal model explicitly represented chronic stress with depressive- or anxiety-like behavior. Other neurological, injury, endotoxin, aging, and healthy-organism comparisons were classified as indirect. Compartment was peripheral for blood or serum, central for brain tissue or neuroimaging, and mixed when both were reported. These rules were fixed before calculation. The complete row-level coding appears in Appendix A and in the accompanying comma-separated file.

The distribution in Table 1 reveals the central interpretive constraint. Only eight comparisons involved humans, and only nine directly concerned affective illness or an affective stress model. TUS and DBS were represented entirely by rodents, whereas the PBM category contained a single aging experiment. Any apparent separation among modalities is therefore partly entangled with disease context and organism. DICA retains these imbalances visibly rather than masking them in a pooled numerical effect.

2.1. Directional Immune Concordance Analysis

The signed response d_i represented whether the reported immune state moved toward or away from reduced pathological inflammation:

$$d_i = \begin{cases} +1, & \text{pro-inflammatory activity decreased or anti-inflammatory activity increased,} \\ 0, & \text{no detectable change or internally mixed direction,} \\ -1, & \text{pro-inflammatory activity increased or inflammatory glial activation rose.} \end{cases} \tag{1}$$

The zero category was deliberately conservative. A row with both favorable and unfavorable analytes was not forced into either sign, and a nonsignificant difference was not interpreted as biological equivalence. The group-level directional mean for a modality or subgroup g was

$$D_g = \frac{1}{n_g} \sum_{i \in g} d_i. \tag{2}$$

This statistic ranges from -1 to $+1$. A value of $+1$ indicates unanimous normalization, a value of 0 indicates balance or indeterminacy, and a negative value indicates that inflammatory activation predominates. It is a direction score, not an effect size; two studies with different cytokine magnitudes can share a sign, and the score cannot estimate clinical benefit.

Sampling uncertainty for D_g was evaluated by resampling the rows within each group 20,000 times with replacement. Percentile limits at 2.5% and 97.5% were retained. The procedure asks how stable the observed mean is to the composition of the small corpus. It does not correct publication bias or restore missing magnitudes.

Table 1. Corpus composition

Modality	Comparisons	Human	Direct affective	Central readout
TMS	3	2	3	1
TES	6	3	2	4
ECT	4	2	3	2
PBM	1	0	0	1
TUS	3	0	0	3
DBS	5	0	0	5
VNS	5	1	1	1
Total	27	8	9	17

2.2. Probabilistic normalization estimate

The probability that a directionally decisive comparison favored normalization was estimated separately from D_g. Let x_g be the number of $+1$ comparisons and y_g the number of -1 comparisons. Null and mixed rows were excluded from this probability but remained in the directional mean. A Jeffreys prior yielded

$$\theta_g \mid x_g, y_g \sim \mathrm{Beta}\left(x_g + \tfrac{1}{2}, y_g + \tfrac{1}{2}\right). \tag{3}$$

Posterior medians and 95% credible intervals were obtained by 200,000 deterministic random draws. The half-count prior prevents a probability of exactly one from being treated as certain when only three or five favorable comparisons exist. No posterior was calculated for PBM because its single row had mixed direction and therefore contributed no decisive observation.

2.3. Translation and compartment experiments

Directional means were compared between direct and indirect affective relevance, human and rodent studies, and peripheral and central readouts. Absolute differences were evaluated with 100,000 label-randomization draws. The null operation preserved the complete set of signed values and group sizes while permuting membership. Mixed-compartment rows were omitted only from the peripheral–central comparison. A separate randomization experiment assessed modality heterogeneity with a weighted between-group sum of squares. These tests were used as compatibility checks, not as claims that the observations were independent randomized samples.

2.4. Adversarial sign fragility

The sign-fragility value F_g measured how many favorable comparisons had to be recoded from $+1$ to -1 before the aggregate sum became nonpositive:

$$F_g = \min\left\{k \geq 0 : \sum_{i \in g} d_i - 2k \leq 0\right\}. \tag{4}$$

Each reversal reduces the signed sum by two. This is intentionally harsher than deleting a study: it asks how much direct contradictory evidence would overturn the group direction. A value of zero means that the observed sum was already nonpositive. The calculation should be interpreted jointly with group size, because a larger corpus can sustain more reversals even when its favorable proportion is unchanged.

2.5. Reproducibility and reporting safeguards

All calculations used Python's standard random-number generator with fixed seed 271828. The corpus, analysis script, machine-readable summary, and figure script are included with the manuscript. The visualizations were generated directly from the coded rows; no synthetic neuroimaging, histology, participant photograph, or device photograph was presented as observed evidence. The study makes no claim of primary clinical recruitment, animal intervention, or laboratory assay. Numerical conclusions are restricted to the direction-coded corpus.

The distinctions in Table 2 prevent the analysis from converting directional evidence into false quantitative precision. Agreement among the directional mean, posterior estimate, translation contrasts, and sign-fragility experiment would support a robust qualitative tendency. Disagreement would indicate dependence on coding, sample composition, or group size and would weaken a mechanistic conclusion.

3. RESULTS

3.1. Overall direction and study-level distribution

Among the 27 comparisons, 19 (70.4%) indicated neuroimmune normalization, five (18.5%) indicated inflammatory activation, and three (11.1%) were null or mixed. The overall directional mean was 0.519, with a 95% bootstrap interval from 0.222 to 0.815. Thus, favorable immune direction predominated across the corpus, and the resampled interval remained above zero. That convergence was not unanimous and did not establish equivalence among biological contexts.

The full distribution in Fig. 1 shows why the pooled tendency requires qualification. Every TUS and VNS row

Table 2. Analytical quantities

Quantity	Purpose	Interpretive boundary
Signed response d_i	Retains normalization, indeterminacy, or activation for each comparison	Does not encode magnitude
Directional mean D_g	Summarizes balance of signs within a group	Does not estimate symptom change
Jeffreys posterior θ_g	Expresses probability of normalization among decisive rows	Excludes null and mixed rows
Bootstrap interval	Quantifies sensitivity to row composition	Does not correct selective reporting
Randomization probability	Tests compatibility with exchangeable group labels	Observations are not randomized trials of modality
Sign fragility F_g	Measures resistance to direct contradictory recoding	Increases with group size

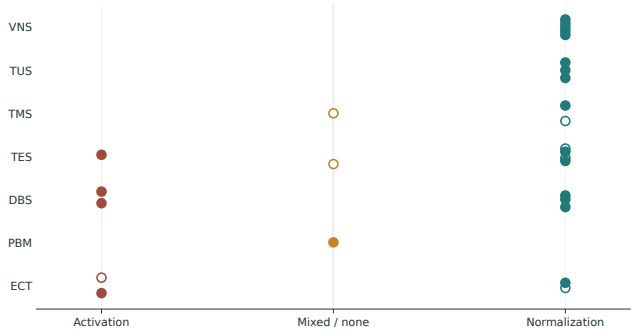

Figure 1. Study-level immune direction.

Table 3. Modality-level directional results

Modality	n	Norm.	Active	D_g	95% bootstrap interval
TMS	3	2	0	0.667	0.000–1.000
TES	6	4	1	0.500	−0.167–1.000
ECT	4	2	2	0.000	−1.000–1.000
PBM	1	0	0	0.000	0.000–0.000
TUS	3	3	0	1.000	1.000–1.000
DBS	5	3	2	0.200	−0.600–1.000
VNS	5	5	0	1.000	1.000–1.000

fell on the normalization side, while ECT split evenly between activation and normalization. DBS combined two activation reports with three normalization reports. TMS and TES contained null findings, and TES also contained an activation result. The single PBM observation was internally mixed. Open circles identify human comparisons; their distribution overlaps rather than separates from the filled rodent observations.

3.2. Modality-specific estimates

VNS and TUS each had a directional mean of 1.000. TMS followed at 0.667, TES at 0.500, DBS at 0.200, and both ECT and PBM at 0. The modality randomization statistic was 3.774, with $p = 0.478$. The observed ordering was therefore compatible with substantial label exchangeability in a corpus of this size. It should be read as a description of present reports, not a verified hierarchy of immune efficacy.

The counts in Table 3 explain the wide uncertainty.

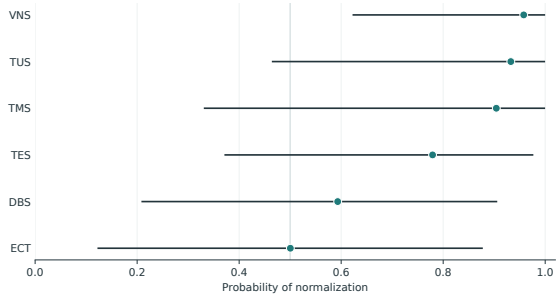

Figure 2. Modality-specific normalization probabilities.

A unanimous direction produces a degenerate row-bootstrap interval when every observed sign is identical, but it does not imply population certainty. The Jeffreys posterior supplies the missing small-sample penalty: a technique with three favorable rows retains more uncertainty than one with five.

Posterior medians in Fig. 2 were 0.958 for VNS (95% CrI 0.622–1.000), 0.933 for TUS (0.464–1.000), 0.904 for TMS (0.331–1.000), 0.779 for TES (0.371–0.977), 0.593 for DBS (0.208–0.906), and 0.500 for ECT (0.122–0.878). PBM had no directionally decisive row and was omitted. The intervals overlap extensively. VNS has the strongest combination of median probability and lower bound, but its five comparisons include only one human and one direct affective row. TUS has perfect observed direction in three indirect rodent models, which is insufficient to infer antidepressant immune target engagement in patients.

3.3. Transfer to affective illness, humans, and compartments

Direct affective comparisons produced five normalization, two activation, and two null results, yielding $D_g = 0.333$ (95% bootstrap interval -0.222 to 0.778). Indirect comparisons produced 14 normalization, three activation, and one mixed result, yielding $D_g = 0.611$ (0.222–0.889). The absolute difference was 0.278, and the randomization probability was $p = 0.454$. The point estimates suggest attenuation when moving into depression, bipolar depression, or chronic affective stress, but the small corpus does not exclude label exchangeability.

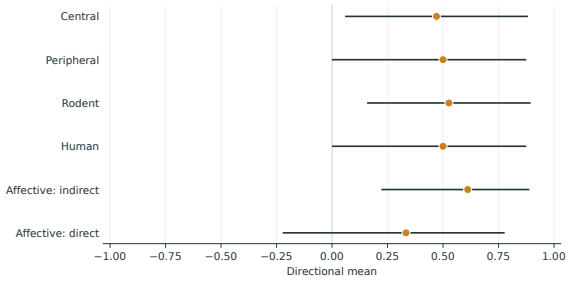

Figure 3. Translation and compartment contrasts.

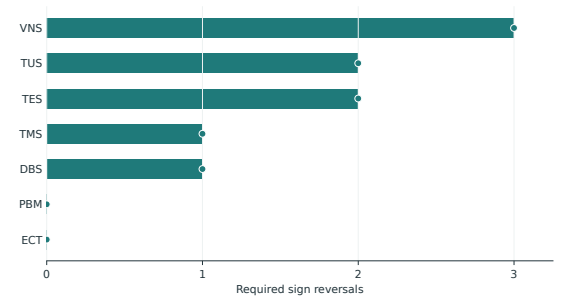

Figure 4. Directional sign fragility.

Human comparisons yielded $D_g = 0.500$ (0.000–0.875), compared with 0.526 (0.158–0.895) in rodents; the absolute difference was 0.026 and $p = 1.000$. Peripheral readouts yielded 0.500 (0.000–0.875), while central readouts yielded 0.471 (0.059–0.882); the absolute difference was 0.029 and $p = 1.000$. These nearly identical point estimates argue against a simple claim that favorable findings arise only from rodent tissue or only from peripheral cytokines. They do not establish cross-compartment correlation within the same participant, because most rows measured one compartment only.

The interval structure in Fig. 3 separates similarity of point estimates from certainty. Human, rodent, peripheral, and central means cluster near 0.5, yet their resampled intervals remain broad. The direct affective interval crosses zero, whereas the indirect interval does not. This pattern locates the principal evidential weakness in disease relevance rather than in a gross human–animal or blood–brain directional reversal.

3.4. Adversarial robustness

The sign-fragility experiment provided a stricter view of stability. VNS required three favorable reports to reverse from normalization to activation before its signed sum became nonpositive. TUS and TES each required two reversals. TMS and DBS required one. ECT and PBM already had nonpositive sums and therefore received zero. Deleting a favorable row would have been less severe; the adopted operation inserted direct contradiction.

The ordering in Fig. 4 modifies the posterior comparison. TMS has a high posterior median among its two decisive favorable rows, yet a single reversal eliminates its positive aggregate because the third row is null. TES has a lower posterior median but can withstand two reversals because four of six rows are favorable. VNS is the most resistant in absolute report count. These differences show why probability, mean direction, and adversarial stability should be interpreted together.

4. DISCUSSION

4.1. Principal answer to the research question

The analysis answers the research question in two parts. Neuroimmune normalization is directionally consistent at the corpus level: more than two thirds of comparisons were favorable, the overall mean was positive, and its row-resampling interval remained above zero. That consistency also did not collapse when evidence was separated into humans and rodents or peripheral and central readouts. In contrast, the evidence does not establish a stable modality hierarchy. Intervals were wide, modality labels were compatible with exchangeability, and the apparently strongest modalities were supported largely by indirect rodent models. Neuroimmune direction can therefore be treated as a cross-modality target-engagement candidate, but not as a stand-alone rule for choosing TUS, VNS, TMS, TES, DBS, ECT, or PBM for an individual with anxiety or depression.

The distinction matters clinically. A biomarker can be useful without identifying the best device. It may indicate that an intervention has engaged a relevant biological state, reveal that an immune-active subgroup differs from an immune-quiescent subgroup, or warn that an acute inflammatory surge has not resolved. Selection among modalities still requires symptom phenotype, circuit anatomy, prior treatment, urgency, tolerability, and access. A patient with severe psychotic depression and imminent suicide risk presents a different decision from a patient with chronic anhedonia and elevated C-reactive protein, even if both show an inflammatory signal.

4.2. Why immune direction converges across dissimilar stimulation

Several mechanisms can produce a shared homeostatic direction without a shared physical action. Repetitive magnetic stimulation can alter astrocytic inflammatory and calcium-related transcription,[26] and higher-frequency stimulation can reduce neurotoxic astrocyte polarization in animal tissue.[27] Theta-burst stimulation can regulate TLR4/NF-κB/NLRP3 signaling and microglial polarization.[28] In a chronic stress model, rTMS reduced hippocampal TNF-α, iNOS, IL-1β, and IL-6 alongside behavioral improvement.[29] Human evidence is directionally mixed: left-prefrontal rTMS decreased IL-1β and TNF-α in refractory depression,[30] whereas bilateral theta-burst stimulation did not produce a significant immune separation from sham in major depression.[31] This combination generated a positive TMS mean but low sign fragility.

Weak electrical stimulation likewise acts through more than cortical excitability. Polarity, montage, frequency, and tissue conductivity influence the field delivered to neurons, glia, and vasculature. In bipolar depression, tDCS altered plasma IL-6 and IL-8 in a sham-controlled design.[32] Another placebo-controlled trial found that plasma biomarker behavior did not reduce to a uniform antidepressant immune signature.[33] The TES corpus therefore contains favorable, null, and unfavorable directions. Its two-reversal fragility reflects the number of favorable observations, while its broad posterior interval cautions against treating all electrical protocols as biologically interchangeable.

ECT is the clearest example of time dependence. Preclinical accounts describe acute innate immune activation followed by neurogenic and regulatory processes.[34] Clinical measurement can capture an early rise in cytokines or a later fall, and those phases need not have the same relationship to symptom change. Reduced inflammatory markers and altered hippocampal volume have been observed during a treatment course.[35] A direction-only synthesis places early activation and later normalization on opposite sides, producing a mean of zero. That result should not be interpreted as absence of immune action. It indicates that sampling time is a defining component of the biological response and that a single pre/post measurement can be misleading.

PBM also illustrates the danger of category-wide conclusions. Its proposed effects involve mitochondrial respiration, redox signaling, perfusion, and secondary inflammatory regulation.[36] The sole in vivo row in this corpus combined an increase in one inflammatory analyte with decreases in others. Assigning zero preserved that internal discordance. A larger PBM literature may eventually justify wavelength-, irradiance-, and target-specific estimates, but the current directional corpus cannot support them.

TUS produced three favorable rodent results. Low-intensity pulsed ultrasound can suppress LPS-induced TLR4/NF-κB signaling and reduce inflammatory cytokines,[37] while transcranial ultrasound reduced neuroinflammation in a chronic Parkinson model.[38] These findings make acoustic stimulation mechanistically attractive because energy can reach deep targets without an implanted lead. Yet none of the three immune rows directly tested anxiety or depression in humans. The posterior lower bound and the direct-affective contrast therefore prevent the perfect observed mean from becoming a clinical superiority claim.

DBS produced both activation and normalization. Implantation can cause gliosis and local inflammatory responses, while chronic stimulation can suppress inflammatory signaling away from the electrode–tissue interface. In a Parkinson model, subthalamic stimulation reduced microglial activation, NF-κB expression, IL-1β, and IL-6 through fractalkine-related signaling.[39] The resulting modality mean of 0.2 captures competing phases and targets rather than weak biological engagement. Future DBS studies in depression should distinguish the surgical interval, stimulation-on interval, anatomical sampling distance, and long-term tissue response.

VNS achieved the strongest combined profile: five favorable rows, the highest posterior median, and three-reversal fragility. The cholinergic anti-inflammatory pathway offers a plausible mechanism, as vagal stimulation can attenuate systemic cytokine release during endotoxemia.[40] Ascending vagal input may also influence locus coeruleus, raphe, thalamic, and limbic activity. Nevertheless, the VNS rows combined cervical, peripheral, auricular, and transcutaneous delivery in different disease contexts. Only one row directly represented chronic stress with affective behavior. The results support prioritized testing of VNS-related immune target engagement, not a claim that VNS is the most effective antidepressant modality.

4.3. Translation from immune normalization to symptom improvement

The lower directional mean among direct affective comparisons is the most consequential result. Immune normalization is easier to demonstrate in models with a strong induced inflammatory insult, such as endotoxin, ischemia, or neurodegeneration. In those settings, the pathological signal is large, the assay is close to the affected tissue, and stimulation can reverse a clear disturbance. Major depression and anxiety are more heterogeneous. Some patients have elevated CRP or cytokines, some show central immune changes without a large peripheral signal, and others show little evidence of an immune-active phenotype. Averaging them can dilute both biological and clinical associations.

This observation favors enrichment rather than universalization. A trial designed to test immune mediation should prespecify an immune-active stratum, but it should also retain an immune-low stratum to determine specificity. Stratification can use a small assay panel rather than a single marker: high-sensitivity CRP, IL-6, TNF-related signaling, and a regulatory marker such as IL-10. The panel should be collected under standardized time-of-day, fasting, infection, medication, body-mass, menstrual, and smoking conditions. Repeated measures are more informative than one pretreatment value because within-person trajectories can separate persistent inflammation from transient noise.

Symptom measurement should be equally specific. Anhedonia, psychomotor slowing, threat sensitivity, sleep disturbance, fatigue, and cognitive control do not necessarily share the same immune coupling. Reward-circuit evidence suggests that inflammation may be especially relevant to anhedonia and motor slowing, whereas amygdala and cingulate effects may be more relevant to threat and social distress. A total depression or anxiety score can conceal a strong association in one symptom domain. The primary clinical endpoint should therefore

be paired with prespecified domain scores and objective behavioral tasks when feasible.

4.4. Temporal and compartment alignment

The similarity between peripheral and central directional means is encouraging but incomplete. It indicates that the corpus does not show a gross contradiction in which blood improves while brain tissue worsens. It does not demonstrate that blood cytokines track microglial state within the same person. Peripheral mediators can reach or signal the brain through endothelial activation, saturable transport, circumventricular regions, immune-cell trafficking, and vagal afferents. Conversely, neural and autonomic output can regulate splenic, adrenal, and vascular immune function. Directional agreement may therefore arise through coupling, parallel response to treatment, or shared regulation.

A decisive study needs synchronized compartments. Blood can be sampled repeatedly before, immediately after, and days after stimulation. Central measurement is harder, but TSPO-PET, magnetic resonance spectroscopy, diffusion-sensitive imaging, or emerging glial ligands can be scheduled at mechanistically chosen intervals. Cerebrospinal fluid may be justified in selected invasive protocols but not as a routine endpoint. The crucial design feature is temporal registration: the brain measure, blood sample, stimulation dose, and symptom assessment must refer to the same biological phase.

ECT demonstrates why this alignment is essential. An acute cytokine rise can coexist with later clinical improvement and later immune normalization. DBS separates surgical inflammation from chronic electrical effects. TMS and TES may produce cumulative plasticity over repeated sessions even when a single session changes excitability. VNS may have immediate autonomic effects and slower network or immune consequences. A study that labels all post-treatment observations as equivalent loses the very dynamics needed to test mediation.

4.5. Interpretation of direction-only evidence

Direction-only synthesis occupies a specific position between narrative description and effect-size pooling. It is most useful when studies repeatedly report whether a biological process increased, decreased, or did not change but use incompatible assays, units, tissues, and sampling intervals. In that setting, retaining sign can reveal whether evidence converges across measurement systems. It cannot reveal whether a small cytokine change and a large microglial change are clinically comparable. The positive overall mean in this study should therefore be understood as cross-assay directional agreement, not as an average anti-inflammatory treatment magnitude.

The separation of D_g from θ_g is important for this reason. The directional mean retains every null or mixed row and describes the observed balance. The posterior probability asks a narrower question among decisive rows and explicitly widens uncertainty when the count is small. TMS illustrates the difference: two favorable and one null comparison yield a high posterior median but only one-reversal fragility. TES has a lower posterior median because it includes an activation report, yet its larger number of favorable comparisons provides greater resistance to reversal. Neither quantity alone captures both proportional consistency and evidential depth.

Adversarial recoding adds another safeguard. Conventional leave-one-out analysis asks whether a conclusion depends on removing an observation. Sign reversal asks whether the conclusion survives the appearance of directly contradictory evidence. This distinction is relevant in neuroimmune research because later work may not merely fail to reproduce a cytokine decrease; it may detect an increase at a different dose or time. A low fragility value signals that such a result would materially alter interpretation. It does not mean that the existing report is unreliable.

Direction-based methods should not replace full quantitative synthesis when compatible effect sizes become available. Their value is transitional and diagnostic: they identify where sign agreement is strong enough to justify harmonized measurement and where biological phase or context already produces contradiction. In the present corpus, that diagnostic function directs attention toward VNS and TUS for confirmatory immune measurement, toward ECT and DBS for temporal separation, and toward direct affective populations for the most urgent expansion of evidence.

4.6. Implications for trial design and treatment selection

The present findings support a longitudinal, compartment-matched trial architecture. Participants should be characterized by symptom domain, immune activity, medication exposure, and circuit phenotype. Stimulation dose should be recorded as delivered rather than prescribed, including electric-field or acoustic-field modeling when relevant. Immune assays should be obtained at an early response phase, an intermediate plasticity phase, and a sustained clinical phase. The analysis should test whether immune change precedes symptom change, whether that temporal association differs by immune stratum, and whether the association is stronger for particular symptom domains.

Mediation should not be inferred from parallel improvement alone. A convincing chain requires stimulation to alter the immune measure, the immune change to predict later symptom change after accounting for prior symptoms, and sensitivity analysis to alternative temporal orders. A sham condition remains important because expectation, sleep, stress, and clinical contact can influence both immune and symptom measures. Protocols should also record anti-inflammatory medication, infection, vaccination, exercise, and circadian timing. These factors can be larger than the device-associated change

in small samples.

For treatment selection, the immediate implication is conservative. VNS and TUS deserve mechanistic prioritization because their observed directions were consistent, but their evidence is not sufficiently direct to guide routine modality choice in anxiety or depression. TMS and TES have more direct affective evidence but also null or unfavorable immune findings. ECT requires phase-specific interpretation rather than a single direction. DBS requires separation of implantation and stimulation. PBM needs a larger in vivo affective corpus. A clinician should therefore select a modality on established clinical indications and use immune measurements, where available, as adjunctive information rather than as a substitute for efficacy evidence.

4.7. Strengths and limitations

DICA has four strengths. It preserves the complete row-level direction when common effect sizes are unavailable, keeps indeterminate findings visible, penalizes small samples through posterior uncertainty, and tests conclusions under direct contradictory recoding. The corpus and scripts make every number traceable. The method also prevents a visually compelling unanimous subgroup from being treated as certain merely because all three available observations point the same way.

The limitations are substantial. Direction coding discards magnitude, variance, dose, and duration. Multiple readouts within a row can be biologically discordant, and assigning zero to mixed direction is only one defensible rule. Study quality, risk of bias, and publication bias were not numerically weighted because comparable assessments were unavailable for every row. Several rows concern diseases other than anxiety or depression. Organism, modality, disease, target, and compartment are not independently distributed. Some studies may contribute related evidence, so randomization probabilities are descriptive compatibility checks rather than conventional inferential guarantees. Unanimous row-bootstrap intervals are too narrow because resampling cannot create unseen contradictory studies; the Jeffreys posterior and sign-fragility experiment partly address this problem but cannot replace new observations.

The method also cannot determine whether immune change mediates symptom improvement. Directional co-occurrence can reflect a common upstream neural effect, regression toward physiological equilibrium, medication change, or nonspecific stress reduction. The corpus lacks participant-level trajectories and does not support individualized prediction. These limitations define the evidential boundary of the conclusion rather than negating the observed cross-modality tendency.

5. CONCLUSION

The paper asked whether neuroimmune normalization remains directionally consistent across neuromodulation modalities, organisms, compartments, and direct affective models, and whether favorable modality profiles withstand contradictory recoding. The answer is that a general homeostatic immune direction is present, but modality superiority is not established. Nineteen of 27 comparisons favored normalization, and the overall directional interval remained positive. Human and rodent directions, as well as peripheral and central directions, were closely aligned. Yet direct anxiety/depression evidence was less stable than evidence from indirect disease models, modality heterogeneity was not supported, and most modality-specific intervals were wide. VNS showed the greatest resistance to sign reversal, followed by TUS and TES, but those results remain constrained by limited direct affective evidence.

Accordingly, inflammatory measurements are best positioned as longitudinal target-engagement indicators, not stand-alone device-selection tests. The critical next experiment is a sham-controlled, immune-stratified neuromodulation study in which delivered dose, symptom domains, blood inflammatory markers, and circuit-proximal neuroimmune measurements are synchronized across acute and sustained phases. Such a design can determine whether immune change precedes and explains clinically meaningful improvement. Until that evidence exists, modality choice should follow established clinical efficacy and safety, while neuroimmune measurements should be used to refine mechanistic understanding and identify the patients in whom inflammation is genuinely treatment-relevant.

COMPETING INTERESTS

The author declares no competing interests.

BIBLIOGRAFIA / REFERENCES

1. Santomauro DF, Mantilla Herrera AM, Shadid J, Zheng P, Ashbaugh C, Pigott DM, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet*. 2021;398:1700–1712.
2. Sinyor M, Schaffer A, Levitt A. The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. *Can J Psychiatry*. 2010;55:126–135.
3. Conroy SK, Holtzheimer PE. Neuromodulation strategies for the treatment of depression. *Am J Psychiatry*. 2021;178:1082–1088. doi:10.1176/appi.ajp.2021.21101034.
4. Cheng Y-C, Kuo P-H, Su M-I, Huang W-L. The efficacy of non-invasive, non-convulsive electrical neuromodulation on depression, anxiety and sleep disturbance: a systematic review and meta-analysis. *Psychol Med*. 2022;52:801–812.
5. Haroon E, Daguanno AW, Woolwine BJ, Goldsmith DR, Baer WM, Wommack EC, et al. Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder. *Psychoneuroendocrinology*. 2018;95:43–49.
6. Osimo EF, Pillinger T, Rodriguez IM, Khandaker GM,

Pariante CM, Howes OD. Inflammatory markers in depression: a meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain Behav Immun*. 2020;87:901–909.
7. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: a meta-analysis. *Eur Neuropsychopharmacol*. 2015;25:1532–1543.
8. Kofod J, Elfving B, Nielsen EH, Mors O, Köhler-Forsberg O. Depression and inflammation: correlation between changes in inflammatory markers with antidepressant response and long-term prognosis. *Eur Neuropsychopharmacol*. 2022;54:116–125.
9. Setiawan E, Wilson AA, Mizrahi R, Rusjan PM, Miller L, Rajkowska G, et al. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry*. 2015;72:268–275.
10. Setiawan E, Attwells S, Wilson AA, Mizrahi R, Rusjan PM, Miller L, et al. Association of translocator protein total distribution volume with duration of untreated major depressive disorder: a cross-sectional study. *Lancet Psychiatry*. 2018;5:339–347.
11. Attwells S, Setiawan E, Rusjan PM, Xu C, Hutton C, Rafiei D, et al. Translocator protein distribution volume predicts reduction of symptoms during open-label trial of celecoxib in major depressive disorder. *Biol Psychiatry*. 2020;88:649–656.
12. Gritti D, Delvecchio G, Ferro A, Bressi C, Brambilla P. Neuroinflammation in major depressive disorder: a review of PET imaging studies examining the 18-kDa translocator protein. *J Affect Disord*. 2021;292:642–651.
13. Munshi S, Loh MK, Ferrara N, DeJoseph MR, Ritger A, Padival M, et al. Repeated stress induces a pro-inflammatory state, increases amygdala neuronal and microglial activation, and causes anxiety in adult male rats. *Brain Behav Immun*. 2020;84:180–199.
14. Nie X, Kitaoka S, Tanaka K, Segi-Nishida E, Imoto Y, Ogawa A, et al. The innate immune receptors TLR2/4 mediate repeated social defeat stress-induced social avoidance through prefrontal microglial activation. *Neuron*. 2018;99:464–479.e7.
15. Wang Y-L, Han Q-Q, Gong W-Q, Pan D-H, Wang L-Z, Hu W, et al. Microglial activation mediates chronic mild stress-induced depressive- and anxiety-like behavior in adult rats. *J Neuroinflammation*. 2018;15:21.
16. Zheng ZH, Tu JL, Li XH, Hua Q, Liu WZ, Liu Y, et al. Neuroinflammation induces anxiety- and depressive-like behavior by modulating neuronal plasticity in the basolateral amygdala. *Brain Behav Immun*. 2021;91:505–518.
17. Patel RR, Wolfe SA, Bajo M, Abeynaike S, Pahng A, Borgonetti V, et al. IL-10 normalizes aberrant amygdala GABA transmission and reverses anxiety-like behavior and dependence-induced escalation of alcohol intake. *Prog Neurobiol*. 2021;199:101952.
18. Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Mol Psychiatry*. 2016;21:1358–1365.
19. Yin L, Xu X, Chen G, Mehta ND, Haroon E, Miller AH, et al. Inflammation and decreased functional connectivity in a widely distributed network in depression: centralized effects in the ventral medial prefrontal cortex. *Brain Behav Immun*. 2019;80:657–666.
20. Harrison NA, Voon V, Cercignani M, Cooper EA, Pessiglione M, Critchley HD. A neurocomputational account of how inflammation enhances sensitivity to punishments versus rewards. *Biol Psychiatry*. 2016;80:73–81.
21. Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biol Psychiatry*. 2010;68:748–754.
22. Hu H, Cui Y, Yang Y. Circuits and functions of the lateral habenula in health and in disease. *Nat Rev Neurosci*. 2020;21:277–295.
23. Wang Y, Qu P, Sun Y, Li Z, Liu L, Yang L. Association between increased inflammatory cytokine expression in the lateral habenular nucleus and depressive-like behavior induced by unpredictable chronic stress in rats. *Exp Neurol*. 2022;349:113964.
24. Ito H, Nozaki K, Sakimura K, Abe M, Yamawaki S, Aizawa H. Activation of proprotein convertase in the mouse habenula causes depressive-like behaviors through remodeling of extracellular matrix. *Neuropsychopharmacology*. 2021;46:442–454.
25. Guo B, Zhang M, Hao W, Wang Y, Zhang T, Liu C. Neuroinflammation mechanisms of neuromodulation therapies for anxiety and depression. *Transl Psychiatry*. 2023;13:5. doi:10.1038/s41398-022-02297-y.
26. Clarke D, Beros J, Bates KA, Harvey AR, Tang AD, Rodger J. Low intensity repetitive magnetic stimulation reduces expression of genes related to inflammation and calcium signalling in cultured mouse cortical astrocytes. *Brain Stimul*. 2021;14:183–191.
27. Hong Y, Liu Q, Peng M, Bai M, Li J, Sun R, et al. High-frequency repetitive transcranial magnetic stimulation improves functional recovery by inhibiting neurotoxic polarization of astrocytes in ischemic rats. *J Neuroinflammation*. 2020;17:150.
28. Luo L, Liu M, Fan Y, Zhang J, Liu L, Li Y, et al. Intermittent theta-burst stimulation improves motor function by inhibiting neuronal pyroptosis and regulating microglial polarization via TLR4/NFκB/NLRP3 signaling pathway in cerebral ischemic mice. *J Neuroinflammation*. 2022;19:141.
29. Tian L, Sun S-S, Cui L-B, Wang S-Q, Peng Z-W, Tan Q-R, et al. Repetitive transcranial magnetic stimulation elicits antidepressant- and anxiolytic-like effect via nuclear factor-E2-related factor 2-mediated anti-inflammation mechanism in rats. *Neuroscience*. 2020;429:119–133.
30. Zhao X, Li Y, Tian Q, Zhu B, Zhao Z. Repetitive transcranial magnetic stimulation increases serum brain-derived neurotrophic factor and decreases

interleukin-1β and tumor necrosis factor-α in elderly patients with refractory depression. *J Int Med Res*. 2019;47:1848–1855.

31. Chou PH, Lu MK, Tsai CH, Hsieh WT, Lai HC, Shityakov S, et al. Antidepressant efficacy and immune effects of bilateral theta burst stimulation monotherapy in major depression: a randomized, double-blind, sham-controlled study. *Brain Behav Immun*. 2020;88:144–150.
32. Goerigk S, Cretaz E, Sampaio-Junior B, Vieira ELM, Gattaz W, Klein I, et al. Effects of tDCS on neuroplasticity and inflammatory biomarkers in bipolar depression: results from a sham-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;105:110119.
33. Brunoni AR, Padberg F, Vieira ELM, Teixeira AL, Carvalho AF, Lotufo PA, et al. Plasma biomarkers in a placebo-controlled trial comparing tDCS and escitalopram efficacy in major depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;86:211–217.
34. Giacobbe J, Pariante CM, Borsini A. The innate immune system and neurogenesis as modulating mechanisms of electroconvulsive therapy in preclinical studies. *J Psychopharmacol*. 2020;34:1086–1097.
35. Belge J-B, van Diermen L, Sabbe B, Parizel P, Morrens M, Coppens V, et al. Inflammation, hippocampal volume, and therapeutic outcome following electroconvulsive therapy in depressive patients: a pilot study. *Neuropsychobiology*. 2020;79:222–232. doi:10.1159/000506133.
36. Caldieraro MA, Cassano P. Transcranial and systemic photobiomodulation for major depressive disorder: a systematic review of efficacy, tolerability and biological mechanisms. *J Affect Disord*. 2019;243:262–273.
37. Chen TT, Lan TH, Yang FY. Low-intensity pulsed ultrasound attenuates LPS-induced neuroinflammation and memory impairment by modulation of TLR4/NF-κB signaling and CREB/BDNF expression. *Cereb Cortex*. 2019;29:1430–1438.
38. Zhou H, Meng L, Xia X, Lin Z, Zhou W, Pang N, et al. Transcranial ultrasound stimulation suppresses neuroinflammation in a chronic mouse model of Parkinson's disease. *IEEE Trans Biomed Eng*. 2021;68:3375–3387.
39. Chen Y, Zhu G, Liu D, Zhang X, Liu Y, Yuan T, et al. Subthalamic nucleus deep brain stimulation suppresses neuroinflammation by fractalkine pathway in Parkinson's disease rat model. *Brain Behav Immun*. 2020;90:16–25.
40. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000;405:458–462.

A. ROW-LEVEL CORPUS

Table 4. Coded in vivo comparisons.

ID	Mode	Population or model	Target	Direction
1	TMS	Refractory depression	Left dorsolateral prefrontal cortex	Normalization
2	TMS	Major depressive disorder	Bilateral dorsolateral prefrontal cortex	No detectable change
3	TMS	Chronic unpredictable mild stress	Vertex	Normalization
4	TES	Bipolar depression	Dorsolateral prefrontal cortex	Normalization
5	TES	Major depressive disorder	Left–right dorsolateral prefrontal cortex	No detectable change
6	TES	Alzheimer disease	Bitemporal cortex	Normalization
7	TES	Vascular dementia	Posterior to bregma	Normalization
8	TES	Healthy rodents	Frontal cortex	Normalization
9	TES	Middle cerebral artery occlusion	Ischemic hemisphere	Activation
10	ECT	Treatment-resistant major depression	Right unilateral or bilateral	Activation
11	ECT	Chronic unpredictable mild stress	Bilateral ear clip	Activation
12	ECT	Depression	Bitemporal	Normalization
13	ECT	Autoimmune encephalomyelitis	Ear clip	Normalization
14	PBM	Aging	Cerebral cortex	Mixed
15	TUS	Middle cerebral artery occlusion	Ischemic hemisphere	Normalization
16	TUS	Lipopolysaccharide challenge	Posterior to bregma	Normalization
17	TUS	Parkinson disease	Subthalamic nucleus	Normalization
18	DBS	Unspecified rat model	Infralimbic cortex	Activation
19	DBS	Unspecified rat model	Subthalamic nucleus	Activation
20	DBS	Fluid percussion injury	Lateral cerebellar nucleus	Normalization
21	DBS	Pilocarpine-induced status epilepticus	Anterior thalamic nucleus	Normalization
22	DBS	6-hydroxydopamine Parkinson model	Subthalamic nucleus	Normalization
23	VNS	Migraine	Cervical vagus nerve	Normalization
24	VNS	Lipopolysaccharide endotoxemia	Peripheral vagus nerve	Normalization
25	VNS	Lipopolysaccharide endotoxemia	Vagus nerve	Normalization
26	VNS	Postoperative cognitive dysfunction	Auricular vagus nerve	Normalization
27	VNS	Chronic stress with constriction injury	Transcutaneous auricular vagus nerve	Normalization

The appendix preserves all 27 analytical units used in every calculation. It also makes the imbalance immediately visible: direct affective evidence is concentrated in TMS, TES, and ECT, while the unanimous TUS direction derives from three indirect rodent models. The main conclusion therefore rests on overall neuroimmune convergence rather than on a cross-device efficacy claim.