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Cross-Modal Circuit Prioritization Identifies a Stable Prefrontal–Amygdalar Control Axis in Bipolar Disorder

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ABSTRACT

Bipolar disorder presents with coupled disturbances of affective regulation, cognition, and psychomotor activity, yet neuroimaging and stimulation studies commonly examine these dimensions separately. A clinically useful circuit account must identify neural elements that recur across dimensions, distinguish depression from mania, and remain stable when influential studies are removed. A study-level bipolar circuit evidence matrix was constructed from 32 investigations comprising 2,614 reported participant records: 10 emotion-connectivity cohorts, 12 cognition-network cohorts, and 10 non-invasive stimulation trials. Regional terms were harmonized into ten circuit elements. Each study received a design coefficient and a logarithmic sample contribution. A cross-domain control-priority score combined evidential prevalence, domain reach, stimulation alignment, and mood-phase specificity. Signed phase loadings quantified depression–mania polarity. Stability was tested through 32 leave-one-study-out runs and three complete stream-deletion runs. The dorsolateral prefrontal cortex (dlPFC) ranked first with a normalized priority of 100 and remained among the leading three elements in every perturbation. The amygdala ranked second (50.31) and retained a leading-three position in 97.1% of perturbations. Salience and sensorimotor networks followed (32.56 and 32.04), whereas default-mode-network priority (31.43) was strongly dependent on the cognition stream. Eight of ten stimulation trials reported symptomatic or cognitive improvement; among depression trials, six of eight were positive. Phase coding separated depression-dominant internal-network loading from mania-dominant sensorimotor loading, while prefrontal–amygdalar coupling showed large opposing values in both phases. The research question is answered by a hierarchical result: bipolar circuit evidence converges most reliably on a prefrontal–amygdalar control axis, with salience, default-mode, and sensorimotor systems determining phase expression. The dlPFC is therefore the most defensible cross-domain perturbation target, but phase-sensitive network state should guide when and how it is engaged.

Keywords: bipolar disorder; functional connectivity; dorsolateral prefrontal cortex; amygdala; default mode network; sensorimotor network; transcranial stimulation

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1. INTRODUCTION

Bipolar disorder is defined by recurrent changes in mood, energy, cognition, and activity, but its disability cannot be reduced to alternating emotional valence. Executive inefficiency, unstable salience attribution, altered reward sensitivity, slowed or accelerated movement, and persistent cognitive impairment frequently cross diagnostic episode boundaries. Neuropsychological meta-analyses have shown that executive function, verbal learning, memory, and social cognition can remain impaired during euthymia, indicating that symptomatic remission does not necessarily restore the neural operations required for everyday functioning.[22,23] At the same time, affective lability can persist between episodes, and psychomotor acceleration in mania or retardation in depression can organize the clinical presentation.[11,12] These observations motivate a circuit question that is broader than the localization of a mood symptom: which neural elements coordinate affective, cognitive, and motor expressions strongly enough to remain plausible intervention targets across heterogeneous studies?

Contemporary models place fronto-limbic dysfunction near the center of bipolar pathophysiology. Ventral prefrontal, anterior cingulate, striatal, hippocampal, and amygdalar abnormalities have been observed during emotional perception and regulation, while lateral prefrontal recruitment is often insufficient when patients must exert deliberate control over affective responses.[2,3] A recurring interpretation is that heightened limbic responsivity is inadequately constrained by prefrontal control. The interpretation is clinically attractive because it links observable emotional lability to a perturbable cortical target. It is nevertheless incomplete. Amygdalar activity differs with task, medication, age, and episode polarity, and fronto-amygdalar coupling can be abnormal even when regional activation is not.[5,6] Longitudinal evidence further suggests that the direction and persistence of amygdalar connectivity change with mood state.[37] A useful account must therefore retain directional and phase information instead of treating every reported alteration as interchangeable.

Large-scale intrinsic networks provide a second level of organization. The default mode network (DMN) supports internally oriented cognition and autobiographical processing; the central executive network (CEN) supports working memory and goal-directed control; the salience network (SN) contributes to the detection of behaviorally relevant events and switching between internal and external processing; and the sensorimotor network (SMN) coordinates exteroceptive and motor operations. Their functions are not confined to a single psychiatric diagnosis. The SN-centered triple-network account explains how an alteration in switching can propagate into executive and default-mode dysfunction,[27] while cortical parcellation work demonstrates that these systems arise from reproducible connectivity organization rather than convenient anatomical grouping.[26] In bipolar disorder, reduced within-network integration and altered cross-network coupling have been described in the DMN, CEN, and SN, including during clinical remission.[10,28–30] Resting-state graph analysis further links distributed organization to cognitive performance.[34] Such results shift attention from isolated lesions toward coordination failures among systems with different temporal and behavioral roles.

Psychomotor expression makes this coordination problem especially consequential. The SMN is not simply an output channel. Its activity is modulated by thalamic, basal-ganglia, salience, executive, and default-mode systems, allowing motor readiness to reflect both environmental demands and internally generated states. Phase-comparative work has described opposite changes in large-scale functional architecture during bipolar mania and depression.[4,39] The balance between DMN and SMN activity has likewise been related to mood polarity, with depression associated with stronger internal orientation and mania with stronger external or motor orientation. Dopaminergic and serotonergic influences can alter this balance through subcortical–cortical pathways,[40] and thalamo-cortical dysconnectivity extends the candidate mechanism beyond a cortical antagonism.[7] Psychomotor findings thus supply a stringent test: a circuit element with high cross-domain importance should connect emotional control to changes in network state and action readiness.

Intervention evidence offers a third level because it asks whether perturbing a candidate region changes clinical or cognitive function. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have most often targeted prefrontal cortex in bipolar depression. Some controlled and open studies report reductions in depressive symptoms or improvement in cognition, whereas others show no separation from sham stimulation.[17–19] Variability can arise from coil geometry, laterality, frequency, medication, diagnosis, episode severity, and the functional connectivity of the stimulated site. Bilateral prefrontal stimulation has also been associated with changes in resting networks and cognition.[20] Circuit engagement is not limited to devices; cognitive-behavioral therapy has shown pooled benefit in controlled bipolar trials and may recruit prefrontal regulation through repeated practice.[16] These findings do not justify a uniform efficacy claim, but they provide an intervention anchor: anatomical importance becomes more convincing when it is supported by both observation and perturbation.

The literature remains difficult to integrate because emotion studies emphasize region-to-region coupling, cognitive studies report network-level abnormalities, psychomotor studies stress phase balance, and stimulation trials report clinical scales. Sample sizes vary by more than an order of magnitude. Conventional narrative aggregation can make a frequently named region appear decisive even when it belongs to only one evidential

stream. Conversely, a region examined in fewer but complementary study types may have greater translational reach. Network science has long emphasized that cognition arises from structural and functional relations rather than isolated centers,[24] and resting-state studies established that distributed synchronization can be analyzed as organized systems.[25] What is still needed for bipolar disorder is an analysis that respects that distributed organization while directly testing cross-domain recurrence and perturbation stability.

The present study asks whether a compact set of circuit elements retains high priority after emotion-connectivity, cognition-network, psychomotor-phase, and non-invasive stimulation evidence are placed on a common scale. The analysis introduces an evidence-weighted control-priority score, signed phase loading, treatment-alignment analysis, and systematic deletion tests. The primary expectation is that lateral prefrontal cortex will show the strongest cross-domain stability because it participates in deliberate emotion regulation, executive control, and stimulation trials. A second expectation is that the amygdala will have high evidential prevalence but lower domain reach, while DMN and SMN contributions will be more phase-sensitive. The goal is not to collapse heterogeneous outcomes into a single effect size; it is to identify which circuit priorities survive heterogeneity and which priorities are conditional on the type of evidence available.

2. MATERIALS AND METHODS

2.1. Research design

The analysis used a study-level dataset containing three complementary streams. The emotion stream comprised ten functional neuroimaging cohorts that examined fronto-limbic coupling during emotional tasks or rest. The cognition stream comprised twelve cohorts that examined regional activity, intrinsic networks, dynamic connectivity, response timing, or transdiagnostic thalamo-cortical organization. The stimulation stream comprised ten rTMS or tDCS trials spanning manic, depressive, and euthymic states. Together these studies contained 2,614 reported participant records. Study names, sample sizes, mood states, acquisition or intervention methods, implicated regions, and directional findings were transcribed from the three tables in the attached review.[1] The citation appears here once because the table contents jointly define the evidence matrix.

Participant totals were treated as reported records rather than unique persons because cross-publication cohort overlap could not be excluded. Emotion cohorts contributed 661 records, cognition cohorts 1,618, and stimulation trials 335. Publication years ranged from 1998 to 2021, with a median of 2016. The unit of analysis was a study record, not an individual participant or image. This distinction prevents ecological estimates from being interpreted as patient-level predictions.

Each record contained the variables `study`, `year`, `n`, `stream`, `mood`, `design`, `method`, `nodes`, `outcome`, and `direction`. Direction was coded as increase, decrease, mixed, phase-opposed, improvement, or null. The coding preserved uncertainty: a report with opposite findings for two connections was not forced into a single positive or negative category. Clinical improvement meant a reported reduction in symptom severity or increase in a named cognitive outcome; null meant no significant difference for the stated primary comparison. No unreported effect magnitude was imputed.

The composition summarized in Table 1 shows why direct pooling of standardized clinical effects was not appropriate. The cognition stream had almost five times as many participant records as the stimulation stream, but its endpoints were primarily imaging quantities rather than treatment response. A sample-count-only synthesis would consequently allow large transdiagnostic cohorts to dominate a question about bipolar treatment relevance. The analysis instead combined sample-sensitive contributions with explicit domain reach and intervention alignment.

2.2. Circuit harmonization

Anatomical and network labels were mapped to ten circuit elements: dlPFC, amygdala, DMN, SMN, CEN, SN, anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), caudate, and thalamus. Dorsal and lateral superior frontal labels were mapped to dlPFC when their reported function concerned executive or regulatory control. Orbitofrontal and medial prefrontal labels were mapped to vmPFC. Inferior frontal, frontoparietal, and posterior parietal findings were mapped to CEN when they represented task-control organization. Insular findings were mapped to SN; limbic labels were mapped to the amygdalar element when the study did not resolve a more specific limbic node. The mapping was intentionally conservative: cerebellar, auditory, visual, and temporal labels were retained in the dataset but contributed to a leading element only when the report explicitly linked them to one of the ten systems.

Harmonization followed functional anatomy supported by prior literature. Prefrontal control and emotion regulation depend on coordinated lateral prefrontal, cingulate, and limbic recruitment.[13,14] The SN is anchored in anterior insular and dorsal cingulate regions and participates in switching between CEN and DMN.[8] The SMN includes motor and sensory areas whose autonomy and integration change with learning and state.[9] These mappings were applied before any ranking was calculated.

2.3. Evidence weighting and control priority

The contribution of study i was

$$w_i = d_i \log(1 + n_i), \tag{1}$$

where n_i is the reported sample size and d_i is a design coefficient. Randomized controlled trials received $d_i =$

Table 1. Composition of the bipolar circuit evidence matrix.

Stream	Studies	Records	Median n	Years	Principal observations
Emotion connectivity	10	661	53.5	2010–2021	Amygdala coupling with orbitofrontal, anterior cingulate, lateral prefrontal, supplementary motor, striatal, and insular regions
Cognition networks	12	1,618	97.0	2004–2021	DMN, CEN, SN, SMN, thalamic, frontoparietal, and limbic activity or connectivity
Non-invasive stimulation	10	335	31.5	1998–2021	Prefrontal rTMS or tDCS associated with depressive, manic, executive, memory, or null outcomes
Total	32	2,614	58.5	1998–2021	Cross-domain circuit and treatment evidence

1.00, other randomized studies 0.86, open studies 0.58, and observational imaging studies 0.72. The logarithm preserved a contribution from larger cohorts without allowing one transdiagnostic sample to overwhelm all smaller phase-specific studies. Coefficients were fixed before ranking and were not fitted to produce a preferred node.

Four node-level quantities were then calculated. Evidential prevalence P_j was the sum of w_i across studies naming node j. Domain reach R_j was the proportion of the three streams in which j occurred. Treatment alignment T_j summed stimulation weights, with an improvement study contributing its full weight and a null study contributing one quarter of its weight; retaining a small null contribution distinguished a tested target from an untested target. Phase specificity H_j gave greater weight to mixed or phase-opposed reports than to unidirectional reports. Each summed quantity was divided by its maximum across the ten nodes.

The control-priority score for node j was

$$C_j = 100\left(0.42\widetilde{P}_j + 0.23R_j + 0.23\widetilde{T}_j + 0.12\widetilde{H}_j\right). \quad (2)$$

The largest coefficient was assigned to recurrence, because replication across studies was the central evidential requirement. Equal coefficients were given to reach and intervention alignment; the smaller phase term rewarded polarity information without allowing it to dominate. A node occurring in only one stream could therefore rank highly through recurrence but could not achieve the maximum score unless it also had treatment and phase support.

2.4. Signed mood-phase loading

Phase separation was evaluated for DMN, SMN, and amygdala–prefrontal coupling. Each directional statement was represented on an axis from depression-dominant (-1) to mania-dominant $(+1)$. A direct phase comparison or a state-specific circuit finding received magnitude 1.0; an indirect state association received magnitude 0.5. A report explicitly comparing phases contributed to both sides, whereas a study without phase resolution did not determine the sign. Each code was multiplied by the study weight in Eq. 1, and the six phase-by-circuit sums were divided by the largest absolute sum. This produced descriptive loadings rather than patient-level effect sizes. The calculation was intended to preserve the direction of the literature and to reveal whether a circuit was strongly represented on one side or on both.

The phase analysis was motivated by evidence that dynamic connectivity differs across bipolar states[31] and that DMN/SMN organization may move in opposite directions in mania and depression.[39] It also accommodated findings that cognitive performance depends on network integrity across diagnoses[32] and that thalamic salience alterations are not unique to bipolar disorder. A circuit could therefore show bipolar phase relevance even when its anatomical abnormality was transdiagnostic.

2.5. Treatment alignment

Stimulation records were grouped by design and episode. Improvement was coded when the named clinical scale decreased or a named cognitive function increased. The ten trials included three randomized controlled trials, three other randomized studies, and four open studies. Depression accounted for eight trials and 298 participant records; mania and euthymia accounted for one trial each. Because stimulation parameters were not uniform and study-level standard errors were unavailable, the analysis reports proportions and participant counts without synthesizing a common clinical effect.

The emphasis on target alignment follows evidence that stimulation response depends on the functional position of the stimulated cortex. Deep rTMS trials have shown both positive and null outcomes in bipolar depression.[18,19] Cognitive safety and improvement have also been studied with tDCS and bilateral stimulation.[20,21]

Pharmacological evidence provides complementary biological plausibility: lithium-related changes in gray and white matter suggest that effective treatment can alter circuit structure and plasticity,[15] while broader biological accounts connect intracellular, transmitter, and network processes.[41] The present treatment analysis was restricted to the stimulation studies included in the matrix so that observational and interventional contributions remained distinguishable.

2.6. Deletion experiments

Priority stability was examined in 35 perturbations. Thirty-two runs removed one study at a time. Three additional runs removed all emotion, cognition, or stimulation records, respectively. For every run, all component quantities were recalculated and the ten nodes were reranked. Stability was summarized by the minimum and maximum priority score and the fraction of perturbations in which a node remained among the leading three. Complete stream deletion is deliberately severe: it reveals whether a leading result depends on one evidential family rather than on cross-domain recurrence.

All computations were scripted in Python. The supplied project includes the CSV matrix, analysis script, calculated node summary, and five figure files. The fixed coefficients, anatomical mapping, and direction codes are visible in these files. Re-running the script regenerates the numerical summary and figures without manual alteration.

3. RESULTS

3.1. Coverage and evidential balance

The 32 studies were distributed evenly by count but not by participant records. Cognition studies contributed 61.9% of the 2,614 records, emotion studies 25.3%, and stimulation studies 12.8%. Median sample size was 97.0 for cognition, 53.5 for emotion, and 31.5 for stimulation. The temporal distribution also differed: stimulation evidence extended back to 1998, whereas the emotion matrix began in 2010. Across all streams, the median publication year was 2016.

The polar distribution in Fig. 1 makes two structural features visible. First, recent large cognition cohorts occupy a dense outer period of the literature, while the intervention stream contains more small studies spread across a longer interval. Second, no temporal period contributes equally to all streams. The cross-domain score therefore should not be read as a historical vote count. Its purpose is to prevent a recent concentration of large cognition samples from erasing the complementary causal relevance of stimulation and the anatomical specificity of emotion-connectivity studies.

Emotion records repeatedly named the amygdala, lateral prefrontal cortex, ACC, and vmPFC. Cognition records were more distributed, with DMN, CEN, SN, SMN, thalamic, and frontoparietal terms. Stimulation records were

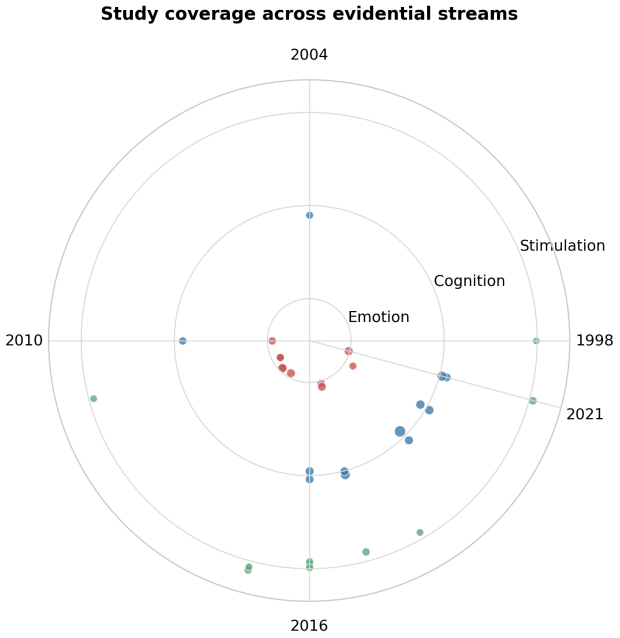

Figure 1. Study coverage by year, sample size, and evidential stream.

anatomically concentrated: nine of ten involved dlPFC directly, and the remaining prefronto-cerebellar study still engaged prefrontal cortex. This concentration increased treatment alignment for dlPFC but did not guarantee its overall rank because recurrence and reach were calculated independently.

3.2. Cross-domain circuit priority

The dlPFC achieved the maximum normalized score of 100.00. Its lead arose from presence in all three streams, strong intervention alignment, and repeated participation in emotional and cognitive control. The amygdala ranked second at 50.31. Its substantial prevalence in emotion studies was moderated by limited direct representation in the stimulation stream. SN (32.56), SMN (32.04), and DMN (31.43) formed a closely spaced middle tier. ACC (30.35), vmPFC (29.84), and CEN (27.22) followed, with caudate and thalamus lower.

The point-range display in Fig. 2 shows that rank and certainty are not identical. The dlPFC interval remained well above most alternatives, even though deleting the stimulation stream reduced its score from 100 to 61.24. The amygdala had a wider range, 15.92–69.33, because removal of emotion evidence sharply reduced its support. DMN and CEN reached zero when the cognition stream was removed, demonstrating that their importance was stream-conditional. In contrast, SN and SMN retained nonzero values because insular, motor, or stimulation associations extended beyond cognition studies.

The stability values in Table 2 resolve the close middle-tier scores by showing top-three frequency. SN remained in the leading three in 77.1% of perturbations, substantially more often than SMN (17.1%) or DMN (5.7%).

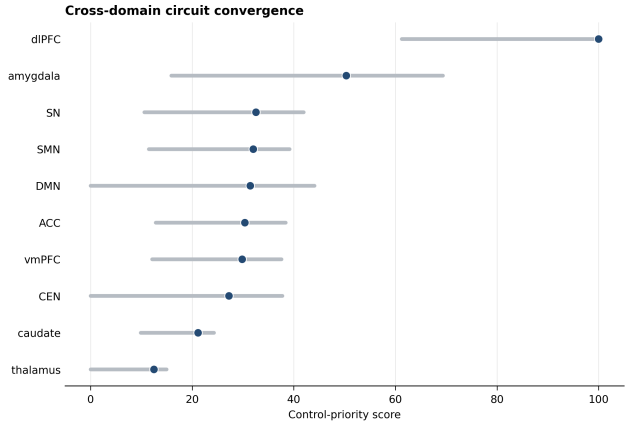

Figure 2. Circuit priority with deletion intervals.

Table 2. Circuit priority and perturbation stability.

Element	Score	Minimum	Maximum	Top-3
dlPFC	100.00	61.24	100.00	1.000
Amygdala	50.31	15.92	69.33	0.971
SN	32.56	10.55	41.92	0.771
SMN	32.04	11.47	39.17	0.171
DMN	31.43	0.00	44.04	0.057
ACC	30.35	12.81	38.37	0.029
vmPFC	29.84	12.13	37.59	0.000
CEN	27.22	0.00	37.76	0.000
Caudate	21.15	9.85	24.28	0.000
Thalamus	12.46	0.00	14.94	0.000

This result indicates that salience organization has more cross-stream resilience than its raw score alone suggests. The thalamus had the lowest score, but this does not imply biological irrelevance. Rather, explicit thalamic naming was sparse within the 32 records, and much of its role was embedded in network descriptions rather than isolated as a target.

3.3. Mood-phase polarity

Signed loadings separated circuits with phase-asymmetric roles. DMN had a larger depression-side magnitude (-0.87) than mania-side value ($+0.63$). SMN showed the reverse asymmetry, with a larger mania-side value ($+0.82$) than depression-side value (-0.44). Amygdala–prefrontal coupling was strongly represented on both sides (-1.00 and $+0.83$), consistent with a control relation that changes across phases rather than disappearing in one phase.

The separation shown in Fig. 3 supports a hierarchical interpretation. DMN and SMN describe the direction of state expression, whereas prefrontal–amygdalar coupling describes a regulatory relation perturbed in both directions. A purely region-based model would miss the opposed internal–external network loading. A purely large-scale-network model would miss the consistent prefrontal–limbic control relation. Combining both levels explains why the dlPFC can remain the leading target while the desired physiological effect differs between a depressive and manic state.

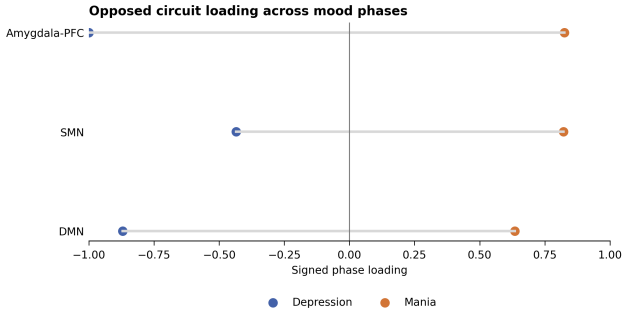

Figure 3. Signed circuit loading in depression and mania.

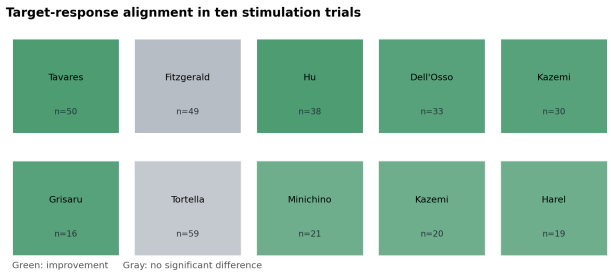

Figure 4. Outcomes of the ten stimulation trials.

3.4. Stimulation alignment

Eight of ten stimulation trials reported improvement in a named symptom or cognitive outcome. Six of eight depression trials were positive, yielding 75% by study count and encompassing 190 of 298 participant records in positive trials. The single mania study reported decreased mania and global-impression scores, and the euthymia study reported improved visuospatial memory and executive function. Two depression studies, totaling 108 participants, reported no significant difference.

The design-stratified values in Table 3 prevent the overall 80% proportion from being treated as an efficacy estimate. Positive findings occurred in two of three randomized controlled trials, all three other randomized studies, and three of four open studies. The participant-weighted picture is more cautious because one of the two null studies had the largest stimulation sample. Design, target definition, and outcome selection therefore remain central to interpretation.

The trial mosaic in Fig. 4 preserves each study rather than merging heterogeneous scales. The two gray tiles are not peripheral exceptions: together they comprise nearly one third of stimulation participant records. Nevertheless, positive tiles span randomized controlled, randomized, and open designs, and they include symptomatic and cognitive endpoints. This distribution explains why stimulation alignment raises dlPFC priority while deletion of the stimulation stream does not eliminate its lead.

Table 3. Stimulation outcomes by design.

Design	Trials	Records	Improvement
Randomized controlled	3	137	2/3
Other randomized	3	79	3/3
Open	4	119	3/4
All designs	10	335	8/10

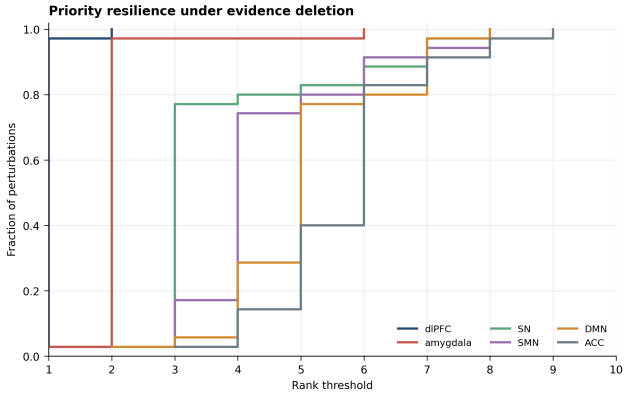

Figure 5. Rank resilience under evidence deletion.

3.5. Priority resilience

The dlPFC remained in the leading three in all 35 perturbations and ranked first in 97.1%. The amygdala remained in the leading three in 97.1% and most often ranked second. SN occupied a leading-three position in 77.1%, while all remaining elements did so in fewer than one fifth of runs. The resilience curves in Fig. 5 show a sharp distinction between the two leading anatomical elements and the phase-related networks.

The cumulative shape adds information beyond the minimum–maximum intervals. Nearly every perturbed ranking placed dlPFC first and amygdala within the first two positions. SN accumulated primarily by rank three, whereas SMN, DMN, and ACC required thresholds of four to six before most perturbations included them. The deletion tests therefore identify a stable core and a conditional state layer rather than a flat list of interchangeable targets.

4. DISCUSSION

The analysis addressed whether a compact set of bipolar circuit elements remains important when emotional, cognitive, psychomotor, and stimulation evidence are integrated and stressed by deletion. The answer is affirmative but hierarchical. The dlPFC and amygdala form a stable cross-domain control axis. SN supplies the most resilient large-scale coordination element. DMN and SMN contribute the clearest mood-phase polarity, while CEN, ACC, vmPFC, caudate, and thalamus provide supporting routes whose rank depends more strongly on the available stream. This organization is more informative than a single diffuse network because it distinguishes a durable perturbation target from the state in which that target operates.

The leading dlPFC result is anatomically and clinically coherent. Lateral prefrontal cortex supports working memory, goal maintenance, reappraisal, and top-down modulation of limbic responses. Functional alterations in bipolar disorder have been observed during emotion regulation and working-memory encoding, including disturbed cortico-amygdalar coupling.[2,14] The region is also accessible to rTMS and tDCS, giving it a direct bridge from mechanism to intervention. This bridge matters: a node can be central in observational imaging yet clinically inaccessible, or accessible yet weakly related to the disorder's core dimensions. The dlPFC ranked first because it satisfied recurrence, reach, treatment alignment, and phase relevance simultaneously.

The amygdala's second position clarifies both its importance and its limitation. It appeared throughout the emotion-connectivity records and participated in relations with orbitofrontal, cingulate, lateral prefrontal, striatal, motor, and insular regions. These findings accord with models in which amygdalar responses acquire pathological significance when prefrontal regulation is weak or mistimed.[5,6] Yet the amygdala was not a direct stimulation target in the included trials and had little independent representation in cognition studies. Its priority therefore fell sharply when emotion records were removed. The result favors indirect modulation through connected cortex over a claim that the amygdala alone organizes bipolar pathology.

The strong SN perturbation stability is a notable finding. Raw priority placed SN only slightly above SMN and DMN, but stream deletion showed that SN more consistently retained a leading-three rank. Salience processes link interoceptive signals, environmental relevance, cingulo-opercular control, and switching between internally and externally oriented networks. Abnormal anterior-insular connectivity can differentiate bipolar depression from unipolar depression and healthy states.[33] Inter-network CEN–SN increases and within-network decreases have also been observed in unmedicated mood disorders.[28] The present result suggests that salience dysfunction is not merely another altered network; it may determine when prefrontal control is assigned to limbic, executive, or motor demands.

DMN and SMN displayed a different evidential signature. Neither matched the deletion stability of dlPFC, amyg-

dala, or SN, but together they carried the strongest phase contrast. The larger depression-side DMN loading is consistent with internally oriented thought, rumination, and failure to suppress task-irrelevant activity. The larger mania-side SMN loading accords with increased action readiness and psychomotor excitation. Functional work has reported opposite large-scale configurations in mania and depression,[39] and SMN cohesiveness has been associated with vulnerability and resilience to bipolar disorder.[38] Dynamic studies further indicate that DMN and SMN connectivity can distinguish depressed from euthymic states.[31] The phase result should therefore be read as a state-coordinate system: it describes the direction of network displacement rather than a fixed trait lesion.

This distinction has consequences for stimulation. If dlPFC is a durable control site but DMN/SMN balance marks current state, identical stimulation for all episodes is unlikely to be optimal. In bipolar depression, an intervention may need to strengthen externally oriented executive engagement and reduce excessive coupling with internally focused activity. During mania, the desired effect may involve constraining motor readiness and aberrant salience while avoiding further activation. This interpretation is compatible with literature suggesting that laterality and protocol differ for depressive and manic symptoms, although the available trials remain too small and heterogeneous for a definitive prescription.[17] Connectivity-guided target selection may be more informative than scalp coordinates alone because two dlPFC sites can occupy different network neighborhoods.

The stimulation results warrant measured optimism. Eight of ten studies reported improvement, but a study-count proportion cannot substitute for a pooled controlled effect. The two null studies included 108 participants, and one was a randomized trial of sequential bilateral rTMS.[19] A deep-rTMS controlled study reported benefit,[18] while tDCS work has generally emphasized cognitive safety and variable clinical response.[21] The present analysis uses these trials to evaluate target alignment, not to estimate treatment efficacy. That role is appropriate because the central question concerns cross-domain circuit priority.

Cognitive findings deepen the interpretation of the prefrontal axis. Cognitive impairment in bipolar disorder has been linked to decreased network efficiency, white-matter disorganization, and altered frontoparietal recruitment.[35] A unified pathophysiological account relates persistent structural damage to cognitive deterioration and superimposed changes in intrinsic activity to episode expression.[36] The current hierarchy is compatible with that account: dlPFC and amygdala represent a recurrent control relation, while network state supplies a fluctuating layer. It also explains why cognition can remain impaired during euthymia. A patient may return toward a neutral DMN/SMN balance without fully restoring lateral prefrontal efficiency or white-matter coordination.

Thalamus and caudate ranked lower than might be expected from established bipolar models. This finding reflects explicit representation within the matrix rather than a rejection of subcortical mechanisms. Thalamocortical disturbances have been demonstrated across bipolar illness and schizophrenia,[7] and monoaminergic modulation of cortico-striatal and motor loops remains central to psychomotor accounts.[40] The lower ranks indicate that the tabulated studies more often reported cortical or large-scale network labels than isolated thalamic or striatal effects. A future dataset with molecular imaging, diffusion tractography, and phase-specific motor measurements could shift these priorities.

Several methodological choices merit attention. Logarithmic sample weighting reduced domination by the largest cohort, and explicit design coefficients preserved the added evidential value of randomization. The coefficients were transparent but not unique. Alternative values could change the middle tier, which is why study and stream deletion were essential. The stable dlPFC and amygdala results are persuasive precisely because they survived severe perturbations. By contrast, DMN and CEN scores fell to zero when cognition evidence was removed, showing that their rank should not be generalized beyond the literature that directly measured them.

The study-level unit limits inference. Reported participant records may overlap across publications, and medication exposure, age, bipolar subtype, episode severity, imaging preprocessing, and stimulation dose could not be modeled consistently. Directional coding does not retain voxel coordinates, standard errors, or effect magnitudes. Mixed findings were preserved but inevitably compress complex spatial results. The phase loadings are literature-derived descriptive values, not estimates of the probability that an individual patient is manic or depressed. No diagnostic classifier was trained, and no clinical decision should be made from the ranking alone.

Another limitation is publication and reporting selectivity. Regions emphasized in study titles, tables, or principal findings are more likely to enter the matrix than negative whole-brain results. The strong dlPFC treatment alignment also reflects historical target choice: prefrontal cortex is accessible, familiar, and widely used, so it has more opportunity to accumulate supportive evidence than a deep node. The deletion experiments address dependence on individual records and streams but cannot correct an unobserved literature. Prospective studies should preregister circuit hypotheses, retain null connectivity results, and report stimulation-site connectivity alongside clinical outcomes.

The analysis nevertheless offers a practical route for study design. A prospective multimodal investigation could measure fronto-amygdalar effective connectivity, SN switching, and DMN/SMN balance in the same participants across depression, euthymia, and mania. Cogni-

tive control, affective reappraisal, and objective motor activity should be acquired together rather than in separate cohorts. Stimulation could then be targeted to an individually connected dlPFC site, with the predicted direction of network change specified before treatment. Such a design would test whether the stable target and conditional state layer identified here correspond to treatment response within persons.

The paper also clarifies the relation between a transdiagnostic network and a disorder-specific application. DMN, CEN, SN, and thalamic changes occur across mood and psychotic disorders, and network integrity can correlate with cognition independent of diagnosis.[32] Bipolar specificity may therefore reside less in the presence of a damaged network than in the temporal combination of prefrontal–limbic control, salience switching, and motor/internal balance. This combination predicts that two people with similar depressive scores could differ in optimal target depending on whether their dominant disturbance is excessive internal coupling, deficient executive recruitment, or weakened emotion regulation.

Finally, the results connect biological description to a falsifiable clinical question. If dlPFC is a stable control site, its leading rank should reproduce when coordinates, effect sizes, and individual-level connectivity are available. If DMN/SMN balance is a phase coordinate, within-person transitions should change that balance in the predicted direction. If SN organizes switching, improvement should be accompanied by more appropriate coupling among salience, executive, and default-mode systems. Failure of these predictions would require the hierarchy to be altered rather than explained away by a broad claim of network dysfunction.

5. CONCLUSION

The research question asked which circuit elements remain priority targets after heterogeneous bipolar evidence is integrated and subjected to systematic deletion. The result is a stable hierarchy, not a diffuse list. The dlPFC is the most defensible cross-domain perturbation target because it connects emotion regulation, executive control, psychomotor coordination, and non-invasive stimulation evidence, and it retained a leading-three rank in every perturbation. The amygdala is the strongest complementary node, while SN provides the most resilient network-level coordinator. DMN and SMN chiefly determine whether the system is displaced toward depression-dominant internal processing or mania-dominant motor engagement.

These findings answer the paper's question by separating target stability from state specificity. A prefrontal–amygdalar axis supplies the durable control relation; salience, default-mode, and sensorimotor systems specify the current operating state. Clinical translation should therefore pair a stable cortical target with phase-sensitive connectivity assessment rather than apply an episode-independent protocol. The supplied evidence matrix and deletion analysis make that conclusion auditable and define direct tests for prospective multimodal and connectivity-guided stimulation studies.

COMPETING INTERESTS

The authors declare no competing interests.

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