NEUROMODULATION

Changing the Conditions of Change

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Contents

Reader's Note

This monograph begins from a simple correction. Neuromodulation is not a remote control for the brain. It does not work by pressing a region and producing a thought, an emotion, or a behavior. It changes the conditions under which distributed neural systems respond, couple, learn, stabilize and move from one state to another.

That correction matters because almost every popular account of the field is tempted by a simpler picture. Dopamine becomes pleasure. Serotonin becomes happiness. a prefrontal coordinate becomes depression. a nucleus becomes craving. a stimulation protocol becomes a fixed dose. a biomarker becomes a personalized answer. Each simplification contains a fragment of truth, yet each becomes misleading when it is treated as the whole mechanism.

The scientific position developed here is therefore deliberately layered. Mechanism, efficacy, safety, durability and translation are kept separate. A finding can be strong at one level and weak at another. A physiological effect can be reproducible without proving therapeutic benefit. A treatment can have clinical efficacy while its microscopic mechanism remains unresolved. A compelling engineering principle can justify a research program without justifying routine clinical use.

The central Flow Hijacked synthesis is called the **Neuromodulatory Ac-**

cessibility Field. It is not presented as an established biomarker or as a literal scalar field measured across the brain. It is a conceptual framework for asking a more useful question: *which states are reachable from here, how difficult are the relevant transitions, which inputs can redirect the system, and what makes a transition persist?* The framework is built from state dependence, network dynamics, plasticity, metaplasticity and control theory. Its value depends on whether it can generate operational predictions rather than merely attractive metaphors.

Throughout the text, four epistemic labels are used. **Established** means supported by convergent high-quality evidence. **Supported synthesis** means that established findings are being integrated through a model that is not itself clinically validated. **Emerging** marks a plausible direction supported by early human evidence. **Flow Hijacked hypothesis** marks a novel conceptual proposal that requires explicit testing.

The literature survey underlying the monograph exceeded 300 screened records across partially independent evidence pools. The 76 anchor sources listed at the end are the high-weight skeleton used to stabilize major claims; they are not the entire screened corpus. The next quality-control stage is designed to audit claim-to-source alignment line by line before public assimilation.

Executive Thesis

The brain is never simply "on." It is always in a state: a moving configuration of excitability, arousal, oscillatory phase, neuromodulator tone, effective connectivity, bodily condition, recent learning and accumulated history. Neuromodulation acts inside that moving configuration. Consequently, an intervention that is physically identical can be biologically different when it reaches the system at a different moment.

This is why state dependence is not a nuisance variable. It is part of the mechanism. It is also why plasticity cannot be treated as an unlimited capacity to change. Plasticity has a history. Prior stimulation, prior activity and homeostatic compensation alter the response to the next perturbation. The system changes not only its state but its *susceptibility to being changed again.*

The same logic scales upward. A clinically meaningful target is usually not an isolated dot. It is a node embedded in a circuit, connected by pathways whose organization differs between people. A local electric, magnetic, acoustic or implanted perturbation matters because of the network into which it enters. The sgACC/BA25 story in depression is instructive precisely because it became more useful when it stopped being treated as a solitary depression center and started being understood as part of a distributed network.

Neuromodulation therefore contains three coupled problems. The first is **access**: can we perturb the relevant system with sufficient precision, depth and safety? The second is **state**: what is the system doing when the perturbation arrives? The third is **learning**: what happens after the perturbation, when the system has to consolidate, compete with old patterns and encounter the world again?

A mature account of the field must hold established treatments and frontier technologies in the same frame without pretending that their evidence is equivalent. ECT and selected TMS protocols have substantial clinical evidence in depression. DBS has meaningful evidence in severe refractory OCD but remains unsettled as routine therapy for treatment-resistant depression and highly experimental in addiction. Implanted VNS may produce durable benefit in some treatment-resistant depression populations, while transcutaneous VNS remains more tentative. Focused ultrasound and temporal interference are scientifically important frontiers, but psychiatric efficacy remains investigational. Closed-loop psychiatric stimulation is an engineering direction with exceptional logic and very limited clinical maturity.

The unifying claim of this monograph is therefore modest but consequential: **neuromodulation is best understood as control of susceptibility, coupling, transition and learning.** It can change a possibility space. It does not, by itself, decide which life should occupy that space.

Part I — What Modulation Actually Means

1. The Brain Is Not in One State

The moving baseline

A treatment is never delivered to an abstract brain. It arrives in a particular nervous system at a particular moment: awake or drowsy, threatened or safe, medicated or unmedicated, recently stimulated or rested, focused outward or absorbed inward. The first mistake in neuromodulation is to treat that moving baseline as noise. The more useful starting point is that baseline state is part of the intervention itself.

Neural state can be described at several levels at once. Membrane excitability matters, but so do population oscillations, arousal, autonomic condition, functional connectivity, neuromodulator tone and the current balance between integration and segregation. None of these variables is the whole state. They are partially observed coordinates of a system whose relevant organization changes with task, body and context. This is why a single resting scan or EEG snapshot is informative without being a complete portrait.

State as a mechanism

Neuromodulatory systems such as locus-coeruleus noradrenaline and basal-forebrain acetylcholine can reorganize gain and network participation without carrying one content-specific message. Arousal changes what competes successfully for processing. Oscillatory phase changes when neuronal populations are more or less excitable. Recent activity changes which synapses or circuits are close to a plasticity threshold. Medication can change the response surface on which a stimulation protocol lands.

Metastable dynamics provide a useful middle ground between a rigid-attractor picture and a story of random fluctuation. The brain can dwell in configurations, leave them, revisit them and alter the ease of those transitions. A depressive, threat-related or craving-related state should therefore not be imagined as a single frozen network. It can be understood as a changed repertoire in which some configurations are entered too readily, others persist too long, and alternative states are comparatively difficult to reach.

What the evidence permits

Human stimulation experiments show state-dependent effects across motor, perceptual and cognitive paradigms. The direction and magnitude of a TMS response can depend on preactivation, oscillatory phase, recent stimulation and task state. These demonstrations establish the phenomenon more strongly than they establish a clinical rule for the optimal state in depression, PTSD or addiction. The latter remains a developing problem.

Network studies in depression and other psychiatric conditions increasingly examine dynamic connectivity, state repertoires and transition structure rather than searching only for one abnormal edge. This move is scientifically important but methodologically delicate. State definitions depend

on preprocessing, temporal resolution and model choice. A cluster found by one pipeline is not automatically a natural kind in the brain.

Clinical reading

A session performed after severe sleep loss, acute stress or a changed medication regimen should not automatically be assumed to be biologically equivalent to the same session on another day. State-aware care does not require measuring everything. It requires refusing to interpret variability as meaningless by default. Recording sleep, substances, medication changes, acute arousal and recent stimulation history may already improve the interpretation of response.

For patients, this encourages modest language. A protocol has a distribution of possible effects, not a guaranteed destination. Nonresponse can reflect many things: target mismatch, dose, state, anatomy, illness heterogeneity, plasticity history or simply the limits of the treatment. Response likewise does not prove that a favorite mechanistic story was correct.

Flow Hijacked lens

The first Flow Hijacked move is to replace a static map with a moving field of accessibility. A state that is currently persistent can make some transitions expensive while making others nearly automatic. Neuromodulation becomes interesting when it changes those transition relationships rather than merely changing a local amplitude.

This is a supported synthesis, not a claim that a literal global potential landscape has been measured. In a nonlinear, nonstationary and partially observed brain, a single scalar potential may not even exist. “Depth” and “barrier” language must therefore be tied either to an explicit reduced model or to the looser idea of effective transition difficulty.

Evidence position: strong for state dependence as a physiological phenomenon; moderate for disorder-specific clinical optimization. Anchor sources: A04, A05, A08, A09, A18, A25, A26.

2. Modulation Is Not Transmission

The postal metaphor breaks

The word neurotransmitter encourages a postal metaphor: one neuron releases a chemical, another receives a message, and behavior follows. That picture is useful at a synapse but too narrow for neuromodulation. Many modulatory systems act diffusely, through receptor families with different intracellular effects, over different time scales, and in ways that depend on what the receiving circuit is already doing.

Modulation can alter neuronal gain, signal-to-noise relationships, synaptic release probability, membrane conductances and the rules that determine whether recent activity will be learned. A chemical signal may change how strongly a population responds to the same input without specifying the content of that input. It may alter the threshold for plasticity, the relative influence of competing signals or the persistence of an action policy.

Receptors, circuits and time

The same transmitter can have opposing effects in different receptor, cell-type and circuit contexts. This is why one-dimensional chemical stories

repeatedly fail. Serotonin is not one operation. Dopamine is not one operation. Noradrenaline is not one operation. Acetylcholine is not one operation. Receptor distribution, projection anatomy, tonic versus phasic release and local microcircuit state all matter.

Broad projections and volume transmission allow modulatory systems to coordinate distributed networks without encoding a specific thought, reward or emotion. A useful distinction is between information content and the conditions under which information is amplified, ignored, learned or linked to action. The distinction explains why a treatment can change the *capacity* to respond before the person reports a new subjective content.

Evidence without slogans

Foundational systems neuroscience strongly supports receptor- and circuit-specific effects for dopamine, serotonin, noradrenaline and acetylcholine. Pharmacological modulation of non-invasive stimulation also shows that background neurochemistry can alter the direction or magnitude of induced plasticity. The interaction is not well captured by simple addition: drug effect plus stimulation effect can become a different event because the drug changes the response function itself.

No high-quality evidence supports slogans such as dopamine equals pleasure or serotonin equals happiness as adequate mechanistic descriptions. These phrases are culturally durable precisely because they compress complexity, but compression becomes distortion when it replaces the actual causal architecture.

Clinical reading

Clinical explanations should avoid promising that an intervention restores a single missing chemical or resets one abnormal switch. Medication and

stimulation can interact because they alter both baseline physiology and the rules through which subsequent perturbations are expressed. When patients ask what a treatment does, the more accurate short answer is often that it changes how circuits respond and learn, not that it inserts a specific feeling.

This also means that medication state belongs inside stimulation studies rather than at the margins. A trial that groups multiple pharmacological backgrounds together may estimate an average clinical effect while obscuring meaningful mechanistic subgroups. That is not a reason to abandon pragmatic trials. It is a reason to distinguish efficacy questions from mechanistic ones.

Flow Hijacked lens

Flow Hijacked treats modulation as a change in the effective flow through which ongoing activity moves. The language is useful only if it remains model-aware: a vector field here is a conceptual representation of changing dynamics, not a literal map measured at every point of the living brain.

The central consequence is that possibility can change before subjective content changes. A system can become more responsive to evidence, more capable of leaving a rigid trajectory or more plastic in the presence of learning without the intervention prescribing what should be learned.

Evidence position: high for receptor- and circuit-specific modulation; high for rejection of one-transmitter/one-emotion narratives. Anchor sources: A01, A02, A03, A06, A13, A14, A15, A67.

3. Plasticity Has a Memory

Change changes the ability to change

Plasticity is often described as the brain's ability to change. That is true but incomplete. Plasticity itself changes. A circuit that has recently been driven strongly may respond differently to the next perturbation. The threshold for potentiation or depression can shift. Homeostatic processes can oppose repeated excitation. The system carries a memory of how change has recently been attempted.

Metaplasticity refers to this change in the propensity for future plasticity. Homeostatic plasticity describes stabilizing processes that prevent activity from drifting indefinitely in one direction. The concepts overlap but are not identical. Together they force a correction to the intuitive dose model: twice the stimulation is not necessarily twice the biological effect.

Sequence and interval

In non-invasive stimulation, priming protocols can reverse, attenuate or amplify later responses. The interval between blocks matters. The order matters. Baseline activity matters. These findings make sequence a

mechanistic variable rather than a scheduling detail.

Plasticity windows also exist across multiple time scales. Millisecond timing can influence synaptic coincidence. Minutes and hours matter for induced after-effects and consolidation. Days and weeks matter for repeated learning, structural adaptation and the behavioral ecology into which the intervention is embedded. A single word, plasticity, therefore covers processes with very different clocks.

Limits of the LTP/LTD analogy

Human stimulation research often uses LTP-like and LTD-like language because some protocols produce changes in excitability that resemble potentiation or depression. The analogy is useful but should not be mistaken for a direct microscopic measurement of synaptic LTP in a living human cortex. The same surface readout can arise from multiple cellular mechanisms.

The evidence for metaplastic and homeostatic effects is nonetheless strong enough to matter. It provides a mechanistic basis for why accelerated schedules need careful spacing and why nominally identical sessions can stop behaving identically across a course of treatment.

Clinical reading

Dose planning should include history. What happened minutes, hours and days before the current session can influence the response. A failure to improve after repeated sessions may reflect target or protocol mismatch, but it can also reflect adaptation, ceiling effects or a shifting state of susceptibility.

Clinically meaningful durability requires more than an acute perturbation.

The new pattern has to survive the return of competing homeostatic and environmental forces. The nervous system is not waiting passively to preserve the state created in a clinic. It continues to regulate itself, learn and encounter old cues.

Flow Hijacked lens

The formal model therefore includes a slower variable, theta, representing effective-connectivity and plasticity history. An intervention can change today's fast state x while also changing H, the rule by which today's activity reshapes tomorrow's response. This is the mathematical place where metaplasticity enters the story.

It also gives a principled reason to care about what happens after a session. If a window has been opened but the old environment immediately rehearses the old trajectory, plasticity can stabilize the familiar solution. Plasticity is not intrinsically therapeutic. It is an amplification of learning capacity whose direction depends on what is learned.

Evidence position: high mechanistically; moderate for precise clinical scheduling rules. Anchor sources: A07, A10, A11, A12, A23, A24, A30, A67.

4. Gain, Uncertainty and Attention

Attention is allocation

Attention feels like a spotlight, but biologically it is not a single beam. It depends on the relative amplification of some signals, suppression of others, expectations about uncertainty and the organism's readiness to act. Noradrenaline and acetylcholine are central to this allocation problem because they can alter the gain and precision of cortical processing across broad regions.

The locus-coeruleus noradrenergic system has been modeled as supporting adaptive gain, shifting the balance between exploiting a current policy and exploring alternatives when conditions change. The model is influential because it links neuromodulation to behavioral flexibility rather than to a single emotion. It should still be treated as a model, not a complete inventory of locus-coeruleus function.

Acetylcholine and relevance

Acetylcholine can sharpen sensory processing, influence cortical state and participate in experience-dependent plasticity, especially when signals are

behaviorally relevant. In many settings it changes what is worth learning from rather than carrying the learned content itself. Noradrenaline and acetylcholine often interact with each other and with ongoing cortical dynamics rather than acting as independent channels.

Arousal is not monotonically beneficial. Very low and very high arousal can both impair selective control, and the optimal range depends on task and person. This nonlinearity is crucial in psychiatry, where hyperarousal and under-engagement can coexist across time in the same individual.

What the evidence permits

The adaptive-gain and uncertainty literatures provide influential mechanistic accounts supported by physiological and behavioral data, but no single theory captures every function of these transmitter systems. Human imaging and electrophysiology show state-linked changes in large-scale network organization compatible with neuromodulatory control of integration and segregation.

Direct clinical manipulation of these systems is already common pharmacologically, yet predicting individual network-level consequences remains limited. A medication can have a reliable average effect while still producing heterogeneous changes in attention, arousal and subjective state.

Clinical reading

In ADHD, depression, PTSD and addiction, attentional capture may reflect different combinations of salience, arousal, expectation and learned value rather than one shared chemical deficiency. Interventions that alter arousal can change whether cognitive or psychotherapeutic material is even processable at a given moment.

This supports measuring functional state when interpreting response, while avoiding the opposite mistake of declaring that one pupil, EEG or heart-rate measure fully identifies the relevant neuromodulatory state. Useful biomarkers will probably be conditional and multimodal rather than universal readouts.

Flow Hijacked lens

Gain is one way a trajectory becomes functionally sticky. Competing inputs may exist but fail to acquire enough effective weight to redirect behavior. Changing gain can expand the set of signals capable of perturbing the current path.

That expansion is not automatically therapeutic. If a system becomes more plastic or more sensitive while the dominant environment remains threatening, compulsive or cue-saturated, the newly amplified inputs may stabilize the wrong trajectory. Accessibility must always be paired with direction.

Evidence position: high for neuromodulatory control of gain and state; moderate for disorder-specific computational interpretation. Anchor sources: A02, A03, A04, A05, A06, A15, A18.

5. Motivation Without a Dopamine Myth

The pleasure shortcut

Dopamine became a cultural shorthand for pleasure because the shorthand is easy to remember. It is also scientifically damaging. Dopamine participates in prediction error, learning, vigor, action selection and motivational salience across circuits that differ greatly in function. Serotonin is similarly impossible to reduce to happiness. Its many receptors and projection systems influence flexibility, patience, aversive learning, mood and behavioral policy in context-dependent ways.

Phasic dopamine signals can encode discrepancies between expected and obtained outcomes, allowing value estimates and action policies to update. But a prediction-error account is not a complete theory of motivation. Tonic signaling, receptor subtype, projection target and circuit history contribute to vigor, effort and the willingness to pursue delayed or uncertain outcomes.

Serotonin and policy

Serotonergic modulation is receptor-specific and can alter synaptic plasticity, behavioral flexibility and the balance between persistence and change. A serotonin increase is therefore not equivalent to adding happiness. The same system can participate in multiple computations depending on receptor, location and time.

This matters clinically because mood is an emergent property of distributed brain-body-environment interaction. A transmitter can influence a component of the system without mapping one-to-one onto the person's felt state.

Addiction and depression

For addiction, the correction is especially important. Craving can persist when immediate pleasure is low because learned incentive value, habit, stress and cue-triggered predictions continue to organize behavior. The person may no longer describe the substance or behavior as enjoyable while the relevant action policy remains highly accessible.

For depression, reduced vigor and future-directed action can involve motivational computations without implying that one neurotransmitter concentration explains the syndrome. A future can remain conceptually visible while becoming dynamically weak: the person can know what would matter and still experience almost no effective pull toward it.

What the evidence permits

Reward-prediction-error evidence is robust, but translating a computational variable into a total account of addiction or motivation would overreach the data. Recent work on serotonergic modulation of plasticity like-

wise supports a role in changing learning conditions rather than a simple mood meter. Clinical pharmacology demonstrates meaningful transmitter effects while simultaneously showing how dose, receptor and time complicate simple stories.

Good psychoeducation should therefore replace both moralizing and chemical slogans with a model of learning under altered value and state conditions. That model is more complex, but it also restores a more realistic account of agency: behavior is constrained by learned accessibility without being reducible to one molecule.

Flow Hijacked lens

Flow Hijacked uses dopamine and serotonin as examples of how the accessibility of actions can be redistributed. A future option can remain cognitively visible while becoming dynamically weak, whereas a familiar high-value action can become rapidly reachable.

The relevant quantity is not pleasure but the changing probability that competing policies gain control. This creates a bridge from neuromodulation to the larger question of why tomorrow sometimes cannot compete with what is immediately available.

Evidence position: high for dopamine learning functions and receptor-specific serotonergic modulation; high for rejecting one-chemical explanations. Anchor sources: A13, A14, A20, A21, A67, A68.

6. The Chemical Ecology of a State

No state is made by one transmitter

No brain state is built by one transmitter. Excitatory and inhibitory signaling, retrograde endocannabinoid control, endogenous opioids, orexin, CRF and multiple peptides shape the background against which dopamine, serotonin, noradrenaline and acetylcholine act. The result is better imagined as a chemical ecology than as a row of independent dials.

Glutamatergic excitation and GABAergic inhibition provide much of the fast synaptic substrate whose balance and timing constrain network stability and plasticity. Yet psychiatric disorders should not be reduced to a single global E/I ratio. Balance is local, dynamic and circuit-specific. A system can be overexcitable in one pathway and under-responsive in another.

Retrograde and bodily modulation

Endocannabinoids act retrogradely at many synapses and can regulate transmitter release, stress adaptation and learning. Endogenous opioids link pain, reward and social-affective processes, demonstrating how bodily

and motivational states can be coupled through common systems. Orexin and CRF illustrate the interface between arousal, stress and motivation, where neuromodulation is inseparable from whole-organism state.

These systems also show why the word "brain" can mislead if it implies isolation. Hormonal, autonomic and immune signals alter neural conditions, while neural modulation changes bodily regulation. The relevant unit is often a brain-body system interacting with an environment.

Perturbation and plasticity

Ketamine research is instructive because a glutamatergic perturbation can be followed by broader plastic and network effects rather than a simple momentary increase or decrease in excitation. The therapeutic discussion therefore shifts from a receptor event to the cascade of susceptibility and learning that follows it.

The same logic applies more broadly. Medication, sleep, stress, substances and stimulation all change the background in which another intervention is received. This is a mechanism question and a safety question. Interactions can alter seizure threshold, arousal, cardiovascular state or cognitive condition even when each component is familiar by itself.

Clinical reading

A useful assessment includes recent biological context rather than treating neuromodulation as isolated from the rest of physiology. Recent substance use, medication changes, sleep, withdrawal, hormonal state and acute illness can all matter. The point is not to build an impossible checklist. It is to recognize that biological dose is conditional.

The ecology metaphor also protects against overclaiming. When a treat-

ment changes several downstream systems, it is usually unsafe to select one observed molecular change and declare it the mechanism. Convergent evidence is required to move from association to causal explanation.

Flow Hijacked lens

The model places m(t), the neuromodulatory and physiological context, beside the fast network state instead of burying it inside unexplained noise. The same intervention u(t) can therefore produce different trajectories under different chemical ecologies.

This creates a direct bridge to Body Before Thought. Autonomic and interoceptive state can alter the initial condition into which deliberate cognitive control acts. Sometimes the system changes before an explanation arrives.

Evidence position: high for state-dependent chemical modulation; moderate for specific cross-system therapeutic inferences. Anchor sources: A07, A15, A67, A68, A69.

Part II — Perturbing the System

7. Magnetic Perturbation

From coil to cortex

Transcranial magnetic stimulation looks deceptively simple from outside: a coil clicks above the scalp and pulses induce current in cortex. Yet the biological dose is not the number printed on a machine. Coil geometry, orientation, anatomy, electric-field distribution, intensity, pulse pattern, baseline state and network connectivity all shape what the cortex actually experiences.

A rapidly changing magnetic field induces an electric field that can depolarize neural elements preferentially according to orientation and local anatomy. Repeated protocols such as rTMS, intermittent theta-burst stimulation and continuous theta-burst stimulation aim to create effects that outlast the pulse train, often interpreted through plasticity-like mechanisms.

The dose is not the dial

Motor threshold is a practical calibration tool, but it is not a universal measure of dose for every cortical target. The motor system is accessible and measurable; a prefrontal therapeutic target has different folding, distance and local anatomy. Electric-field modeling makes visible why two people can receive the same machine setting and experience different intracranial

fields.

Dose also includes time. Pulse frequency, burst structure, total pulses, inter-session interval and number of sessions interact with state and plasticity history. A protocol name compresses all of these dimensions into a label and can create false confidence that the biological event is standardized.

Established efficacy, incomplete mechanism

rTMS and TBS have an established evidence base in depression, with sham-controlled trials, meta-analyses and safety guidelines supporting clinical use for selected protocols. Physiological studies support plasticity-related after-effects, but the direction and magnitude of those effects vary substantially between and within people.

Connectivity-based targeting and individualized electric-field modeling are scientifically compelling. They improve the plausibility that the intended network is being engaged. Yet a better mechanistic target does not automatically translate into a larger average clinical effect, and current meta-analytic evidence does not establish universal superiority of personalized rTMS targeting over fixed approaches.

Clinical reading

TMS should be presented as a course of repeated circuit perturbations with probabilistic benefit rather than as a procedure that directly stimulates a happiness center. Clinicians need to distinguish device settings from delivered field, delivered field from target engagement, and target engagement from clinical outcome.

Safety is generally favorable in appropriately screened populations, while

seizure risk, hearing protection, medication changes and protocol-specific limits remain important. Accelerated protocols increase convenience and may speed response, but they make spacing and cumulative plasticity especially important scientific questions.

Flow Hijacked lens

TMS is a clean illustration of the coupling term G in the Flow Hijacked model. The effect of external input depends on geometry, state and network position. A pulse can be physically identical while its effective perturbation differs because the receiving system has changed.

The target therefore becomes a state-sensitive network entry point rather than simply a coordinate. The deepest question is not "where did the pulse land?" but "what transition did this perturbation make more or less likely in this system at this time?"

Evidence position: high for selected depression protocols and safety frameworks; moderate for specific plasticity mechanisms and individualized superiority. Anchor sources: A23, A24, A25, A27, A31, A32, A33, A34.

8. Electric Rhythms

A family, not one treatment

Electrical stimulation replaces the loud click of TMS with weak currents applied through scalp electrodes. The family name hides substantial differences. Direct current shifts membrane polarization subtly, alternating current attempts to interact with ongoing rhythms, random-noise stimulation distributes energy across frequencies, and temporal interference seeks to create a lower-frequency envelope at depth through intersecting high-frequency fields.

These approaches are often grouped as non-invasive brain stimulation, but their mechanistic questions differ. tDCS is especially state-dependent because it generally biases excitability rather than forcing spikes. tACS makes phase and frequency central. tRNS raises hypotheses involving excitability and stochastic resonance. Temporal interference is primarily an engineering strategy for deeper access whose human feasibility is advancing faster than evidence for psychiatric treatment.

tDCS and modest average effects

Individual-participant meta-analytic evidence supports a modest antidepressant effect for tDCS. That is clinically meaningful without being dramatic. The literature also contains heterogeneity in montage, current,

session number, medication status and severity. Small average effects are especially sensitive to these differences.

The correct interpretation is neither dismissal nor enthusiasm. tDCS is a plausible and relatively accessible intervention with evidence of benefit in some settings. It is not a precise remote control and not every home-use implementation reproduces research conditions.

tACS and tRNS

For tACS, the central scientific question is interaction with endogenous rhythms. If stimulation is delivered at a frequency that matches or competes with ongoing activity, phase alignment may matter as much as nominal current. Closed-loop phase-triggered stimulation is therefore conceptually attractive, though clinical psychiatric evidence remains early.

tRNS psychiatric studies show promising signals but a smaller, more heterogeneous evidence base. The parameter space is large, and mechanistic language should remain conservative. A noise-based waveform can alter cortical responsiveness without proving a specific stochastic-resonance mechanism in every therapeutic application.

Temporal interference

Temporal interference is one of the most interesting deep non-invasive concepts because it attempts to exploit the interaction between high-frequency fields to create a lower-frequency modulation envelope at depth. Human studies now support feasibility and physiological effects. That is not equivalent to established selective treatment of deep psychiatric circuits.

Field distribution, cellular sensitivity and the relation between physical envelope and neural response remain active research questions. The cor-

rect status is emerging technology with high strategic value, not routine psychiatric therapy.

Flow Hijacked lens

Electrical approaches make timing visible. If a system is oscillatory, there may be moments when a perturbation couples strongly and moments when the same perturbation is poorly aligned. The control problem is therefore not only how much energy is delivered but when the system is susceptible.

This is where open-loop stimulation begins to approach adaptive stimulation: measure phase or state, infer a window, perturb, then measure again. The clinical promise is substantial, but the evidence hierarchy must move with it.

Evidence position: moderate for tDCS antidepressant efficacy; low-to-moderate for psychiatric tACS/tRNS; emerging for temporal interference. Anchor sources: A35, A36, A37, A38, A39.

9. The Seizure as Treatment

Why ECT forces humility

Electroconvulsive therapy is uncomfortable for simplified stories because it is both clinically powerful and mechanistically plural. A controlled therapeutic seizure can produce rapid improvement in severe depression, including presentations in which delay itself carries major risk. Yet no single molecular, network or endocrine explanation has earned the right to be called *the* mechanism of ECT.

This is a useful lesson for neuromodulation as a whole. Clinical efficacy does not wait for complete mechanistic understanding. A treatment can be established through convergent outcome evidence while the causal chain from intervention to durable recovery remains partly unresolved. The reverse is also true: an elegant mechanism does not guarantee a useful treatment.

A system-wide perturbation

ECT differs from focal cortical stimulation because the seizure is a large-scale dynamical event. It changes network activity, neuroendocrine state,

cerebral perfusion and multiple plasticity-related pathways. Neuroimaging studies repeatedly report structural and functional changes after treatment, but the mapping between those changes and symptom improvement is inconsistent. Volume change is not automatically therapeutic mechanism.

The seizure itself also cannot be reduced to "rebooting" the brain. That metaphor suggests erasing and restarting, whereas ECT acts on a system that retains learning, identity and history. A better description is a powerful perturbation followed by a period of reorganization and plastic adaptation.

Efficacy and cognition

ECT remains among the most effective acute treatments for severe and treatment-resistant depression. The evidential question is therefore not whether it can work, but how to optimize efficacy while reducing burden, relapse and cognitive adverse effects. Electrode placement, pulse width, dose relative to seizure threshold and treatment frequency all influence the trade-off.

Cognitive effects require nuance. Transient confusion and memory disturbance are real, and autobiographical memory complaints can be clinically important. At the same time, severe depression itself impairs cognition, and improvement in illness can improve several cognitive domains. Long-term safety syntheses do not support simplistic claims that ECT inevitably causes progressive global cognitive decline, but individual memory experiences must not be dismissed by averages.

MST as a refinement strategy

Magnetic seizure therapy attempts to induce a therapeutic seizure with more focal electrical activation than ECT. The rationale is that seizure efficacy might be preserved while reducing unwanted cognitive effects through a different spatial distribution. Comparative evidence is growing, but the evidence base is much smaller than for ECT. MST should therefore be described as promising rather than equivalent or superior by default.

This is an example of a recurring engineering strategy in neuromodulation: preserve the causal ingredient thought to matter while reducing collateral engagement. Whether the assumed ingredient is correct must then be tested clinically rather than inferred from elegance.

Flow Hijacked lens

ECT demonstrates that a large perturbation can alter a pathological trajectory without specifying a single local target. In the accessibility framework, the intervention may temporarily reorganize the transition structure of the system and create a period in which other states become reachable. The durability question then becomes central: what makes the system remain in a healthier repertoire once the acute perturbation has passed?

That question naturally leads to continuation treatment, medication, sleep, social ecology and learning. Opening a transition is not the same as stabilizing the destination.

Evidence position: high for ECT efficacy; moderate for specific mechanisms; emerging-to-moderate for MST comparative advantage. Anchor sources: A40, A41, A42, A43, A44, A45.

10. The Vagus as a Plasticity Gate

A nerve that crosses levels

The vagus nerve is compelling because it links bodily regulation, brainstem neuromodulatory systems and cortical plasticity. Implanted VNS was first established in epilepsy and later used in treatment-resistant depression. Transcutaneous approaches attempt to reach auricular or cervical branches without surgery. A separate line of work pairs brief vagal stimulation with specific behaviors to bias plasticity toward the activity occurring at that moment.

These are not one therapy. Chronic implanted VNS, transcutaneous VNS and precisely paired VNS should be separated because their doses, evidence and intended mechanisms differ.

Chronic VNS in depression

Implanted VNS for treatment-resistant depression is notable for a response profile that may be slow and durable in some patients. Long-term observational evidence suggests benefit in selected populations, but the evidential structure differs from a large short-term sham-controlled drug trial.

Surgery, device burden and delayed onset all change the risk-benefit calculation.

The mechanism is also distributed. Vagal afferents influence brainstem nuclei that project broadly, including noradrenergic and cholinergic systems involved in arousal and plasticity. The intervention therefore illustrates how a peripheral input can modify central susceptibility without being reducible to a direct cortical target.

Transcutaneous VNS

Meta-analytic signals for taVNS in depression are encouraging, but evidence quality remains lower and protocols differ in stimulation site, frequency, intensity, control condition and treatment duration. Ear stimulation is not biologically synonymous with implanted VNS. The temptation to transfer confidence from one modality to another should be resisted.

Blinding is also difficult when sensation differs between active and control conditions. Small studies can overestimate benefit, particularly when outcomes are subjective and expectations are strong. The appropriate status is emerging, with a need for larger, better standardized trials.

Pairing and targeted plasticity

The most conceptually important VNS work may come from rehabilitation. When brief vagal stimulation is repeatedly paired with successful movement or sensory events, plasticity can be biased toward the active circuit. The principle has strong translational support outside psychiatry: *timing can convert a global modulatory signal into task-specific learning.*

Psychiatric extrapolation is plausible but not yet established. Pairing VNS with extinction learning, exposure, cognitive work or social signals may

be mechanistically attractive, but each pairing requires its own clinical evidence. A mechanism proven in motor rehabilitation cannot simply be declared therapeutic in PTSD or addiction.

Flow Hijacked lens

Paired VNS provides a concrete example of changing H, the learning rule, while experience supplies the content. The stimulation does not encode the movement or memory. It marks a window in which the coincident event receives enhanced plastic weight.

This distinction is central to the Neuromodulatory Accessibility Field. Modulation can open a gate; experience determines what passes through it. The ethical and therapeutic implication is that context is not decoration around a biological treatment. Under some conditions, context is part of the causal intervention.

Evidence position: moderate for durable benefit from implanted VNS in selected TRD populations; low-to-moderate for taVNS depression; high for the paired-plasticity principle outside psychiatry. Anchor sources: A56, A57, A58, A59, A60.

11. Deep Access

The depth problem

Many psychiatric hypotheses involve deep structures and pathways that are difficult to influence selectively from the scalp. This creates a trade-off. Implanted DBS offers direct, chronic access with precise electrode placement but requires neurosurgery. Focused ultrasound offers the possibility of deep, non-invasive perturbation but remains a young therapeutic field in psychiatry. The technical ability to reach a target and the clinical evidence for treating a disorder must be evaluated separately.

Depth is not synonymous with importance. A superficial cortical node can influence a deep circuit through connectivity, and a deep target can fail if it is the wrong network entry point. The relevant problem is access to a causal circuit, not prestige attached to anatomical depth.

DBS and the lesson of pathways

Deep brain stimulation delivers electrical pulses through implanted electrodes. In movement disorders, decades of experience have shown that outcome depends not only on nucleus labels but on precise engagement of pathways. Psychiatry is learning the same lesson. Tractography and connectomic analyses increasingly identify bundles whose engagement predicts outcome more strongly than distance from a named coordinate.

For severe refractory OCD, sham-controlled and individual-participant evidence supports a meaningful therapeutic effect in carefully selected patients. The treatment remains invasive and specialized, but it has crossed a stronger evidential threshold than many other psychiatric DBS applications.

Depression and addiction

DBS for treatment-resistant depression has produced striking responders, informative long-term cohorts and influential circuit models. It has also produced negative or mixed randomized results. The correct conclusion is not that DBS failed or that it is established. The field remains investigational, with target selection, phenotype, network engagement and trial design still unresolved.

DBS for addiction is earlier still. Human reports are small, heterogeneous and often uncontrolled. Nucleus accumbens targeting is mechanistically attractive because of reward and action-selection circuitry, but the ethical stakes are high and the clinical evidence does not justify routine use.

Focused ultrasound

Low-intensity focused ultrasound can reach deeper structures with millimeter-scale physical focusing that is difficult for conventional TMS or scalp electrical stimulation. Human studies increasingly demonstrate physiological modulation, and early psychiatric pilot work is appearing. Safety syntheses are encouraging within studied parameter ranges, while long-term standards, skull modeling, dose metrics and psychiatric efficacy remain under development.

The technology deserves serious attention precisely because its potential is real. That is also why restraint matters. First-in-human feasibility is not

treatment efficacy, and short follow-up cannot establish durable safety.

Flow Hijacked lens

Deep access changes the coupling matrix G: it creates new routes by which an external controller can influence a system. But control remains network-dependent. A deep coordinate is useful only if changing activity there changes the transition structure relevant to the patient's problem.

The future is therefore likely to combine access with state estimation: not merely stimulating deeper, but stimulating the right pathway at the right time with evidence that the intended circuit has actually changed.

Evidence position: moderate-to-high for DBS in severe refractory OCD; low-to-moderate/investigational for TRD; low for addiction DBS; high technical potential but low-to-moderate psychiatric efficacy evidence for LIFU/tFUS. Anchor sources: A46, A47, A48, A50, A51, A61, A62, A63, A64, A65, A66.

Part III — The Target Is a Circuit and a Time

12. From Dot to Network

The coordinate is not the target

Brain stimulation historically encourages coordinates because coordinates are actionable. A surgeon needs a trajectory. A TMS operator needs a scalp location. An engineer needs a field model. But the clinical target is rarely the coordinate itself. It is the pattern of connections that makes perturbation at that location consequential.

This distinction became especially visible in depression. Dorsolateral prefrontal TMS sites associated with better outcomes tend to have particular functional relationships to subgenual cingulate regions. DBS response likewise appears related to engagement of specific white-matter pathways rather than merely occupying a labeled nucleus.

BA25 without a depression center

The subgenual anterior cingulate, often associated with BA25, is one of the most important nodes in modern depression circuitry. It is also one of the easiest nodes to oversimplify. BA25 should not be described as "the depression center." It participates in a network involving medial and lateral prefrontal cortex, limbic structures, striatum, thalamus and autonomic regulation.

Its value is relational. A cortical target can be useful partly because of how it is connected to this deeper network. A DBS contact can be useful because of which fibers pass nearby. The mechanistic unit therefore shifts from point to circuit.

Functional connectivity and causality

Functional connectivity is statistical dependence, not causal influence. Two regions can correlate because of common input, global state or indirect pathways. Connectivity-guided targeting gains credibility when it converges with lesion mapping, tractography, stimulation effects and prospective outcomes.

This is why connectomics should neither be dismissed as correlational nor promoted as causal by default. The strongest claims arise when multiple methods constrain the same circuit hypothesis.

Individual anatomy

People differ in cortical folding, white-matter anatomy and functional network organization. A group-average coordinate is therefore an approximation. Personalized MRI, tractography and electric-field modeling can reduce some of this mismatch. The open question is how much of that improved anatomical precision produces additional clinical benefit in routine populations.

The answer may differ by disorder and technology. In DBS, millimeters can determine fiber engagement and outcome. In TMS, network-level targeting may matter while individual functional scans introduce their own measurement noise. Personalization must improve the signal more than it adds instability.

Flow Hijacked lens

A network target is a control point: a location where perturbation has leverage over transitions that matter. High leverage is not identical to high activity. A relatively quiet node can be strategically important if it sits on pathways that constrain the flow between states.

This is the natural bridge to network control theory, but the mathematics must be treated carefully. Controllability metrics depend on an assumed network model, often linearized and simplified. They are hypotheses about leverage, not direct measurements of psychological control.

Evidence position: high for network relevance; moderate-to-high for selected connectivity targets; model-dependent for formal controllability claims. Anchor sources: A16, A17, A19, A21, A31, A33, A50, A51, A54, A55.

13. The State You Stimulate Matters

The same pulse, a different system

If state dependence is real, treatment design should eventually become state-aware. The obvious difficulty is deciding what state means in practice. Is it oscillatory phase? arousal? task engagement? autonomic state? symptom intensity? medication level? recent sleep? a multivariate latent variable? The answer is likely to differ by intervention and target.

The safest claim is not that one universal state marker exists. It is that response depends on the system into which stimulation is delivered, and that some of those dependencies can be measured.

Phase and excitability

In motor and perceptual systems, stimulation effects can depend on oscillatory phase and preactivation. A population closer to threshold responds differently from one that is inhibited or engaged in a competing computation. This creates a rationale for EEG-triggered and phase-locked stimulation.

Yet phase is not destiny. Scalp EEG is an imperfect projection of distrib-

uted sources, phase estimates contain uncertainty, and deep targets may not be represented cleanly. Closed-loop timing must therefore demonstrate that the measured signal predicts a meaningful response, not merely that it is technically trackable.

Arousal, stress and medication

A person arriving for treatment after sleep deprivation or acute stress is not in the same physiological state as after restorative sleep. Nor is a patient who has just changed benzodiazepine, anticonvulsant or stimulant exposure. These variables can alter cortical excitability, seizure threshold, attention and plasticity.

The mechanistic relevance is clear even when the clinical effect size is uncertain. Trials and clinics should document state-changing factors sufficiently to interpret outliers and safety events. Over time, such data may reveal subgroups in which state-aware scheduling improves outcome.

Priming and task engagement

State can also be deliberately created. A cognitive task, memory reactivation, exposure cue or motor action can preactivate a circuit before stimulation. This raises the possibility of targeting not only anatomy but an *active computation*. The intervention may then preferentially influence the network that is currently engaged.

Evidence is strongest for the principle in experimental paradigms. Clinical pairings remain heterogeneous. The field should resist assuming that activating a symptom before stimulation is always beneficial; it could strengthen, destabilize or do nothing depending on timing and plasticity rules.

Flow Hijacked lens

The Flow Hijacked model makes initial condition x0 explicit. Accessibility is conditional on where the system starts. A transition that is easy from one state may be difficult from another even under the same input.

This offers a testable design principle: stratify or trigger treatment based on measured state and ask whether the same nominal intervention produces more predictable transitions. The key is prospective validation, not retrospective storytelling.

Evidence position: high for physiological state dependence; emerging for robust clinical state-triggered psychiatric algorithms. Anchor sources: A25, A26, A52, A53, A67, A73.

14. Dose Is Also Time

Beyond intensity

Medicine often represents dose as an amount. Neuromodulation makes that representation incomplete. The same number of pulses can be delivered in different burst structures, at different frequencies, across different intervals and over different numbers of days. Because plasticity is history-dependent, time becomes part of dose.

This is most visible in accelerated TMS, where several sessions are delivered in one day. The appeal is obvious: if treatment can be compressed safely, relief may arrive faster and access may improve. But compression changes the biological problem because sessions can interact before previous effects have stabilized.

Spacing and metaplasticity

Inter-session interval can determine whether repeated perturbations accumulate, saturate or recruit homeostatic opposition. The optimal spacing is unlikely to be universal across protocols. It may depend on intensity, target, medication and baseline physiology.

This creates an important distinction between *calendar dose* and *effective biological dose*. Two treatment courses with equal total pulses can generate

different trajectories because their temporal structure differs.

Accelerated TMS and SNT

Stanford neuromodulation therapy and related accelerated iTBS approaches have produced rapid antidepressant responses in controlled studies. These results are among the most striking recent developments in non-invasive psychiatric stimulation. Larger replication and dose-response work strengthen the case that the effect is not merely a single-site anomaly.

At the same time, specialized targeting, high pulse counts, intensive schedules and limited long-term comparative data mean that the literature should not be compressed into a claim that more sessions per day are always better. The mechanistic contribution of connectivity targeting, spacing and total dose remains partly entangled.

Durability

Rapid response and durable response are different outcomes. A treatment can move the system quickly and still require maintenance, medication, behavioral change or repeated courses to prevent return. Durability should therefore be measured explicitly rather than inferred from acute remission.

The same principle applies across ECT, VNS, DBS and emerging technologies. Each modality has its own temporal signature: immediate perturbation, delayed adaptation, cumulative effect and relapse dynamics.

Flow Hijacked lens

The accessibility framework naturally includes horizon T. A transition can become highly reachable over hours without remaining reachable over

months. Control cost can fall temporarily and then rise again as the system re-equilibrates.

Time therefore belongs inside the mechanism, not just on the appointment schedule. The question is not only whether an intervention works but when, for how long, and how the history it creates changes the next intervention.

Evidence position: moderate-to-high for accelerated iTBS/SNT antidepressant efficacy; high for temporal dependence in plasticity; incomplete for universal spacing rules. Anchor sources: A10, A11, A12, A28, A29, A30.

15. The Promise and Limits of Personalization

Personalization is not one thing

"Personalized neuromodulation" can mean anatomical targeting, functional-connectivity targeting, tractography, individualized electric-field modeling, EEG-guided timing, symptom-specific targets, biomarker selection or individualized dose. These are different interventions under one attractive label.

The scientific case for personalization is strong at first principles. Brains differ. Fields differ. Networks differ. Symptoms differ. It would be surprising if one coordinate and one dose were optimal for everyone. But plausibility is not the same as demonstrated clinical superiority.

Measurement noise is part of personalization

Individualization adds measurements, and measurements have error. Resting-state functional connectivity varies across time and pipeline. Tractography contains false positives and false negatives. Electric-field models depend on segmentation and conductivity assumptions. EEG biomarkers drift with state and artifact.

A personalized method helps only when the information it adds exceeds the uncertainty it introduces. Repeating an unstable individual measure can be worse than using a robust population target.

What the current evidence says

Connectivity-based targeting has strong mechanistic support and has helped organize successful TMS and DBS findings. Individualized sgACC anticorrelation and tract engagement are important research directions. Yet a 2025 meta-analysis comparing personalized and fixed rTMS targeting did not establish convincing overall superiority of personalization.

That result should not be read as evidence that personalization is useless. It is evidence that the current heterogeneous package called personalization has not yet produced a uniform clinical advantage. Better subgroups, better measurements or better algorithms may change the conclusion.

Biomarkers and prediction

A predictive biomarker must do more than correlate with outcome in the data used to discover it. It should generalize prospectively, add value over clinical predictors, remain sufficiently stable for the intended decision and ideally connect to a mechanism that explains why acting on it helps.

Psychiatric neuromodulation contains many candidate biomarkers and few that meet all of these standards. Within-person biomarkers may still be valuable for adaptive stimulation even when they do not generalize as diagnostic markers across people.

Flow Hijacked lens

Personalization can be understood as estimating the local geometry of accessibility for a particular system. The goal is not to create a unique story for every patient but to estimate which perturbation has leverage given this anatomy, this state and this history.

The framework predicts that useful personalization may need to be *conditional* rather than static. The best target could change as the system changes. That possibility leads directly to closed-loop control.

Evidence position: strong scientific rationale; mixed evidence for average clinical superiority; emerging for adaptive, state-conditional personalization. Anchor sources: A27, A32, A33, A50, A51, A52, A53, A54, A55.

Part IV — Adaptive Psychiatry

16. Measure, Infer, Intervene, Measure Again

From protocol to controller

Most clinical neuromodulation is open loop. A protocol is selected, delivered and repeated while outcome is measured relatively slowly. Closed-loop neuromodulation changes the architecture: the system is sensed, a relevant state is inferred, stimulation is adjusted, and the response is sensed again. The ideal is not simply automation. It is feedback control.

The control-theoretic logic is compelling because psychiatric symptoms fluctuate, neural states drift and the relationship between device setting and neural effect is not fixed. If the system changes, a fixed controller may eventually become poorly matched to the state it is trying to influence.

What must be measured

The hardest problem is often not stimulation but sensing. A useful closed-loop signal must be measurable with adequate signal-to-noise, related to the state that matters, available at the right temporal scale and sufficiently stable to guide action. A biomarker that predicts depression severity once a month may be useless for millisecond stimulation timing. A biomarker

that tracks a local field potential beautifully may be clinically irrelevant if it does not map onto the pathological process.

Implanted systems have an advantage because they can record from deep targets continuously. Scalp EEG, autonomic signals and behavior are less invasive but noisier and more indirect. Multimodal sensing may eventually outperform any single channel, at the cost of complexity and data burden.

Proof of concept in psychiatry

Personalized closed-loop stimulation in treatment-resistant depression has produced landmark proof-of-concept cases in which an intracranial biomarker was linked to symptom state and stimulation was delivered adaptively. These reports matter because they demonstrate feasibility. They do not yet establish a general treatment class.

The gap between a remarkable N-of-1 and scalable clinical psychiatry is large. Biomarkers may differ between people. Implantation is invasive. Symptoms evolve. Algorithms can drift. A controller that learns can also make errors in ways that are difficult to inspect.

Adaptive circuit targeting

The broader field is moving toward adaptive circuit targeting: combine anatomy, connectivity, sensing and symptom structure to decide not only where but when and how to stimulate. This direction is likely to blur the boundary between device and model. The therapeutic object becomes a closed-loop system composed of sensors, inference, controller, actuator and patient.

That shift creates new regulatory questions. What is the treatment if an algorithm updates itself? How should version changes be validated?

Which part of the loop is responsible when outcome changes? How should false detections be handled?

Flow Hijacked lens

Closed loop is the most direct engineering expression of the Neuromodulatory Accessibility Field. Estimate the current state, infer whether a maladaptive transition is imminent or a therapeutic window is open, perturb the system, then update the estimate.

But the field is not mature enough for the conceptual elegance to be confused with established clinical superiority. The next advance is not merely better stimulation. It is better state estimation with prospective evidence that the resulting feedback policy improves outcomes that matter to patients.

Evidence position: high as an engineering rationale; proof-of-concept but sparse psychiatric clinical evidence. Anchor sources: A16, A17, A22, A49, A52, A53, A76.

17. When Stimulation Meets Experience

The intervention does not end when the device stops

Neuromodulation is usually discussed as if the important event ends when the session ends. Plasticity research suggests a different possibility. A perturbation can alter what the system is ready to learn from next. If so, the experience surrounding or following stimulation can become part of the causal chain.

This does not mean that every therapy should simply be combined with stimulation. It means that timing between biological susceptibility and experience is a testable variable.

Psychotherapy pairings

A recent meta-analytic literature on rTMS combined with CBT in depression suggests a small-to-moderate incremental benefit in some comparisons. That is important but not universal. The result does not prove that all stimulation plus psychotherapy pairings are synergistic, nor does it reveal a single mechanism.

Combination studies are difficult because both interventions have dose,

timing and fidelity. Was cognitive work performed during stimulation, immediately after it or on separate days? Was the relevant circuit engaged? Did the psychotherapeutic task change? Did improvement reflect added treatment time rather than a mechanistic interaction? These are answerable design questions.

Memory reactivation and reconsolidation

A particularly attractive idea is to reactivate a pathological memory and then stimulate while the trace is labile. Systematic evidence for TMS combined with memory reactivation or reconsolidation paradigms is currently small and heterogeneous. The mechanistic logic is strong enough to justify research, not strong enough to claim reliable rewriting of traumatic or addictive memory.

Reconsolidation has boundary conditions. Not every retrieval destabilizes a memory. Prediction error, age and strength of the memory, context and timing can determine whether updating occurs. An intervention that misses the relevant window may have no effect or may simply reinforce retrieval.

Context and meaning

The broader lesson extends beyond formal psychotherapy. Set, expectation, therapeutic relationship, environmental safety and post-treatment behavior can influence what is learned when plasticity is altered. This is visible in psychedelic research, ketamine-plus-psychotherapy studies and rehabilitation paradigms, although each field has different evidence quality.

Context should not be used as a vague explanation for every outcome. The rigorous question is whether a defined contextual manipulation changes the

effect of a defined biological perturbation relative to appropriate controls.

Flow Hijacked lens

In the formal model, stimulation can change H, the learning rule, while experience supplies structured input to x. A window of increased accessibility without a directional signal can lead anywhere, including back toward the dominant old attractor.

This is why "opening the brain" is not a sufficient therapeutic concept. A treatment should be judged by the state transitions and learning it actually supports, not by plasticity in the abstract.

Evidence position: moderate for specific rTMS+CBT depression combinations; low-to-moderate for memory-reactivation/TMS as a general clinical strategy; strong as a mechanistic principle that plasticity interacts with experience. Anchor sources: A58, A59, A67, A68, A69, A70, A71, A72, A73.

18. Four Stress Tests

Why diagnoses are not enough

A framework is useful only if it survives contact with different problems. Depression, OCD, PTSD and addiction place distinct demands on neuromodulation. They differ in symptoms, time course, learning history, circuit hypotheses and outcome measures. Treating them as the same network disorder would be as misleading as treating them as four entirely unrelated diseases.

The value of a cross-diagnostic lens is to ask the same control questions while allowing different answers: which states dominate, which transitions fail, what maintains the pattern, where can the system be perturbed, and what must be learned afterward?

Depression: inaccessible futures

In depression, the relevant problem may include persistent negative self-referential states, reduced reward responsiveness, altered cognitive control and diminished future-directed vigor. Network findings implicate interactions among default-mode, salience, executive and limbic systems rather than one depression circuit.

TMS, ECT and VNS provide different forms of evidence that changing cir-

cuit dynamics can improve severe symptoms. Yet the treatment response cannot be reduced to normalizing one connection. Some patients improve rapidly, some slowly, some not at all, and relapse remains a separate dynamical problem.

OCD: pathological precision and loops

OCD offers a stronger current case for psychiatric DBS. Recurrent obsessions and compulsions can be described as high-cost failures of stopping, uncertainty resolution and action selection, involving cortico-striato-thalamo-cortical circuitry. Deep stimulation may alter the dynamics of these loops in severe refractory cases.

The success of DBS in selected patients does not imply that OCD is a single loop. Symptoms are heterogeneous, targets vary and behavioral learning remains important. The intervention changes circuit conditions within a disorder that is also maintained by avoidance and reinforcement.

PTSD: threat accessibility

PTSD is a natural state-dependence problem. Threat-related states may become too accessible and persistent, while safety learning and contextual discrimination fail to exert sufficient control. Arousal and memory reactivation can drastically alter the state into which stimulation is delivered.

Network meta-analytic evidence suggests potential for several neuromodulation approaches, but the literature is smaller and less mature than depression. Pairing stimulation with exposure or memory work is theoretically attractive and empirically unsettled.

Addiction: action under learned value

Addiction tests every part of the framework. Cues, stress, habit, reward prediction, withdrawal and social environment change accessibility over minutes to months. Craving is not located in one center. It emerges from distributed motivational, salience, executive and interoceptive systems interacting with learned history.

TMS studies show signals of benefit across substance-use disorders, but heterogeneity in targets, substances and outcomes is substantial. DBS and focused-ultrasound work in addiction remain early. The clearest lesson is that perturbing reward circuitry without changing learning and environment is unlikely to be sufficient.

Flow Hijacked lens

Across the four stress tests, the same abstract language acquires different content. Depression may involve compressed access to future-directed states. OCD may involve over-stabilized error and checking loops. PTSD may involve rapid entry into threat configurations and poor contextual exit. Addiction may involve disproportionately accessible high-value trajectories under cue or stress.

The framework earns its keep only if these distinctions generate different measurements and interventions. If the same metaphor explains everything without risking falsification, it explains nothing.

Evidence position: high for several depression modalities, moderate-to-high for DBS in selected severe OCD, moderate/heterogeneous for PTSD stimulation, and heterogeneous/emerging across addiction technologies. Anchor sources: A19, A20, A21, A35, A42, A46, A47, A48, A54, A55, A72, A73, A74.

Part V — Flow Hijacked Synthesis

19. The Neuromodulatory Accessibility Field

A conceptual object, not a discovered substance

The Neuromodulatory Accessibility Field is the central Flow Hijacked proposal of this monograph. The name is intentionally ambitious and must therefore be paired with an equally explicit limitation: no such field has been validated as a single measurable biological quantity. It is a supported synthesis intended to organize existing facts about state dependence, network dynamics, plasticity, control and learning.

The framework asks a question that standard target language often misses. From the system's present condition, which neural and behavioral states are reachable over a relevant time horizon? How likely are transitions? What perturbation is required? How does recent history alter the answer? What happens to learning after the transition?

A multi-timescale representation

Let x(t) represent a fast neural or network state. Let m(t) represent neuromodulatory and physiological context. Let theta(t) represent slower effective-connectivity, plasticity and accumulated history. Let u(t) repre-

sent an external intervention and xi(t) unresolved endogenous variability.

A deliberately generic stochastic system can be written as:

$$\mathrm{d}x = F(x;\theta,m)\,\mathrm{d}t + G(x;\theta,m)u(t)\,\mathrm{d}t + \Sigma(x,m)\,\mathrm{d}W_t,$$

with a slower adaptation rule

$$\mathrm{d}\theta = \varepsilon H(x,\theta,m,u,\mathrm{history})\,\mathrm{d}t, \qquad 0 < \varepsilon \ll 1.$$

This is not offered as a fitted whole-brain model. Its purpose is conceptual hygiene. F separates intrinsic flow from the external intervention. G represents state-dependent coupling. Sigma makes variability explicit. H gives plasticity and metaplasticity a separate place rather than hiding them inside the fast dynamics.

Accessibility

For a target set of states Omega and time horizon T, define a conceptual accessibility quantity

$$A_T(\Omega \mid x_0,m,\theta,u) = \Pr\{\exists t \le T : x(t) \in \Omega\}.$$

A complementary control-cost expression is

$$E^*(\Omega) = \inf_u \int_0^T \|u(t)\|^2\,\mathrm{d}t,$$

subject to reaching Omega under the assumed model.

These quantities are model-dependent. They are not literal brain energy,

and they are not directly observable without specifying a state representation, dynamics and measurement model. Their value is that they force a clearer question than "did the region activate?"

Five routes by which accessibility can change

Neuromodulation can alter F by changing intrinsic flow, effective coupling or dwell times. It can alter G by making the system more or less responsive to a given input. It can alter Sigma by changing variability or exploration within physiological limits. It can alter H by changing plasticity rules and learning windows. And through distributed network coupling it can alter the effective geometry of a target, so that the same local perturbation has a different global consequence.

Each route suggests observables: changed dwell time, changed transition probability, changed response to an identical perturbation, altered learning after stimulation, altered dose needed to reach a network state, or hysteresis after repeated treatment.

Basin language with a guardrail

Attractor, basin and barrier language can be useful when it describes an explicit reduced model or serves as a careful metaphor for persistence and transition difficulty. It becomes misleading when it implies that the living brain is governed by one global scalar potential landscape. Neural systems are nonequilibrium, nonlinear, non-normal and partially observed. In many models, a true potential does not exist.

Where a barrier is discussed, it should therefore mean an effective transition difficulty or a quasipotential under stated assumptions, not stored psychological energy. The mathematical restraint is part of the concept, not a limitation to be hidden.

Three time scales

Fast dynamics unfold over milliseconds to seconds: phase, excitability and immediate gain. Intermediate dynamics unfold over seconds to hours: arousal, neuromodulator tone, drug state, task context and acute stress. Slow dynamics unfold over days to months: synaptic and circuit plasticity, consolidation, habit, metaplasticity and behavioral ecology.

State dependence follows naturally from the coupling among these scales. It is not an experimental inconvenience added to an otherwise static treatment model.

The testable core

The Flow Hijacked hypothesis is that clinically useful neuromodulation can often be understood as a change in state accessibility rather than simply local activation. That hypothesis is worth keeping only if future studies can operationalize the states, transitions and costs in ways that predict outcomes better than simpler models.

The proper ambition is therefore not to defend the metaphor. It is to make the metaphor lose its necessity by turning it into measurable hypotheses.

Evidence position: supported synthesis grounded in state dependence, plasticity and network-control literatures; the Neuromodulatory Accessibility Field itself remains a Flow Hijacked conceptual proposal. Anchor sources: A08, A09, A16, A17, A18, A20, A21, A22.

20. Opening a Door Is Not Choosing a Destination

The moral error in a technical fantasy

The most dangerous fantasy in neuromodulation is not that the technology will fail. It is that a sufficiently precise technology could decide what a healthy life should be. Better targeting, deeper access and closed-loop control can change neural conditions. They cannot answer the normative question of which goals, relationships, identities and futures deserve to be stabilized.

This is not a philosophical decoration. It is a practical boundary. A biomarker can indicate a pattern associated with symptom severity. It cannot determine whether a person's grief is meaningful, whether a relationship should continue, what kind of life is worth pursuing or which sacrifice is justified.

Agency after biological change

Neuromodulation can alter the ease with which action becomes possible. A severely depressed person may regain energy before meaning returns. A person with OCD may experience reduced compulsive pressure before rebuilding trust in uncertainty. A person with addiction may experience less cue-driven urgency while still needing a social world, routines and commitments that can compete with old trajectories.

These gaps matter. The intervention changes the conditions of agency; it does not replace agency. In some cases, this is precisely why the biological intervention is valuable: it may restore enough flexibility for psychological and social work to become possible again.

Identity and autonomy

Implanted and adaptive devices make identity concerns especially visible. Patients may ask whether a changed mood is truly theirs, whether a device controls them, or whether turning stimulation off would return an earlier self. These questions should not be dismissed as misunderstandings. They are part of the treatment experience.

Closed-loop systems intensify the issue because an algorithm may detect and intervene before the person consciously recognizes a state. That can be therapeutic and unsettling at the same time. Consent must therefore address not only surgical risk but the logic of sensing, adaptation and control.

Neuroprivacy and data

Adaptive psychiatry creates data that are unusually intimate. Neural recordings, mood labels, contextual metadata and behavioral patterns can

reveal states that patients may not wish to share beyond care. Security and governance are therefore part of clinical safety.

A system that senses continuously can also change the therapeutic relationship. Who owns the data? Who can inspect algorithmic decisions? Can a patient contest a model that labels a state as pathological? What happens if commercial incentives encourage more sensing than care requires?

Equity and access

The field also risks a familiar pattern: high-cost personalization and invasive technologies may concentrate in specialist centers while basic evidence-based care remains inaccessible. A technically superior intervention that reaches very few people can coexist with population-level failure.

Equity should therefore be included in the concept of optimization. The best treatment is not defined only by response rate under ideal conditions. Burden, cost, geography, maintenance and opportunity cost matter.

The final distinction

Neuromodulation can change susceptibility, coupling, transition and learning. It can open a door. But an open door has no direction by itself.

This is where the neuromodulation monograph meets Existential Re-Orientation. The biological question is how a trapped system becomes changeable. The existential question is what becomes worth changing toward. Flow Hijacked needs both questions because recovery without flexibility can become impossible, while flexibility without direction can remain empty.

The mature promise of neuromodulation is therefore neither mind control nor mechanical repair. It is more modest and more human: to alter the

conditions under which a person and a nervous system may once again learn, choose, connect and move.

Evidence position: ethics and governance are established necessities; specific identity effects and future governance models remain context-dependent. Anchor sources: A22, A49, A53, A75, A76.

Appendix A — Evidence Architecture

The evidence strategy for this monograph was designed to prevent a common failure in interdisciplinary neuroscience: a strong mechanistic paper being used as proof of clinical efficacy, or a positive clinical trial being used as proof of a favored molecular story. Five evidence axes are therefore kept separate.

Mechanism asks whether the proposed causal process is supported. **Efficacy** asks whether the intervention improves clinically meaningful outcomes relative to an appropriate comparator. **Durability** asks whether benefit persists after the acute perturbation. **Safety** asks about acute and long-term harms, including cognition and device burden. **Translation** asks whether the result generalizes across people, centers and real-world conditions.

The screened literature exceeded 300 records across relatively distinct pools: nonpharmacological depression neuroplasticity studies, TMS in substance-use disorders, homeostatic and metaplastic NIBS experiments, human focused-ultrasound reports, tDCS trials, VNS plasticity studies, tractography-informed DBS studies, ECT molecular-imaging work, tRNS psychiatry, temporal interference, OCD DBS, TRD DBS, addiction DBS,

taVNS, PTSD stimulation, memory-reactivation paradigms, adaptive stimulation, safety and neuroethics.

The count is not obtained by mechanically summing review sample sizes. Overlap was assumed. The purpose of the broad survey was to create a pool larger than the requested floor so that weak, duplicated or irrelevant material could be removed without threatening coverage.

Evidence tiers

Tier A includes rigorous guidelines, consensus safety papers, high-quality meta-analyses, individual-participant meta-analyses, well-powered sham-controlled randomized trials with replication, and landmark mechanistic work that remains coherent under later evidence.

Tier B includes strong systematic reviews, adequately powered randomized trials, multicenter cohorts, convergent connectomic or tractographic studies and replicated physiological findings.

Tier C includes smaller randomized trials, open-label cohorts, single-center biomarker work, correlational imaging and feasibility studies. These sources can support emerging hypotheses but should not carry strong efficacy claims alone.

Tier D is hypothesis-generating: case reports, uncontrolled pilots, small first-in-human studies, preclinical evidence used in clinical contexts and theoretical papers without empirical validation.

A study can be Tier A for one claim and irrelevant to another. A rigorous physiology experiment can strongly establish state dependence while saying little about remission. A large efficacy trial can prove benefit without identifying the exact biological mediator.

Down-weighting rules

Claims were down-weighted when conclusions depended on tiny samples, unclear control conditions, extreme heterogeneity, unreplicated biomarker discovery, commercial or consumer claims, purely anatomical targeting presented as outcome evidence, or review conclusions that exceeded the quality of their included studies.

The governing rule is simple: **no evidence axis may substitute for another.**

Appendix B — Claim-Level Evidence Map

Claim 1: Neuromodulation is state dependent

Evidence position. Strong mechanistic, moderate-to-strong human physiological evidence; clinical optimization evidence still developing.

Confidence. High for the phenomenon, medium for specific therapeutic algorithms.

Boundary condition. State markers differ by modality and disorder; no universal "optimal state."

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 2: Plasticity history changes future responsiveness (metaplasticity)

Evidence position. Strong experimental human NIBS literature plus consensus/review evidence.

Confidence. High mechanistically, medium clinically.

Boundary condition. Protocol-to-protocol transfer is limited; direction can vary by timing/intensity.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 3: Neuromodulatory transmitter systems regulate gain, coupling and plasticity rather than mapping one-to-one onto emotions

Evidence position. Strong basic/system neuroscience.

Confidence. High.

Boundary condition. Receptor and circuit specificity prevents simplistic "chemical X = function Y" language.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 4: Network configuration matters for stimulation response

Evidence position. Strong convergent connectivity/connectomic evidence; growing clinical targeting literature.

Confidence. High conceptually, medium-to-high for selected targets.

Boundary condition. Functional connectivity is method-sensitive and not equivalent to causal influence.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 5: rTMS/TBS is clinically effective for depression

Evidence position. Established through multiple sham-controlled trials/meta-analyses and guideline adoption.

Confidence. High.

Boundary condition. Magnitude, durability and response vary by protocol and population.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 6: Accelerated/SNT-like schedules can produce rapid antidepressant effects

Evidence position. Multiple controlled studies and recent meta-analysis.

Confidence. Moderate-to-high.

Boundary condition. Specialized protocols, sample sizes and durability limit broad generalization.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a

clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 7: Personalized rTMS targeting is superior to fixed targeting

Evidence position. Not established overall; meta-analysis does not show convincing superiority despite strong mechanistic rationale.

Confidence. Low/inconclusive for superiority.

Boundary condition. "Personalized" includes heterogeneous methods; future subgroups may benefit.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 8: tDCS has antidepressant efficacy

Evidence position. Modest average benefit in IPD meta-analysis.

Confidence. Moderate.

Boundary condition. Small effect; remission signal less consistent; protocol heterogeneity.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 9: tACS/tRNS have psychiatric therapeutic value

Evidence position. Emerging/mixed.

Confidence. Low-to-moderate depending indication.

Boundary condition. Parameter space large; many studies small.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 10: ECT is a highly effective intervention for severe depression, while exact mechanisms remain incompletely resolved

Evidence position. Strong clinical evidence; broad mechanistic but non-unitary literature.

Confidence. High efficacy, medium mechanism specificity.

Boundary condition. Cognitive adverse effects require nuanced presentation; not reducible to a single mechanism.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 11: MST may preserve efficacy with a different cognitive/seizure profile than ECT

Evidence position. Growing comparative evidence.

Confidence. Moderate/early.

Boundary condition. Smaller evidence base than ECT.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a

clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 12: DBS is a meaningful intervention for severe refractory OCD

Evidence position. Sham-controlled/IPD and long-term evidence.

Confidence. Moderate-to-high in carefully selected refractory cases.

Boundary condition. Invasive, small populations, specialized centers.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 13: DBS for TRD is established routine therapy

Evidence position. Mixed/investigational; open-label signals stronger than randomized evidence.

Confidence. Low-to-moderate for routine efficacy.

Boundary condition. Target, phenotype and network selection remain unresolved.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 14: DBS for addiction is clinically established

Evidence position. Very early, mostly small and uncontrolled human literature.

Confidence. Low.

Boundary condition. High relapse and major selection/ethical issues.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 15: Implanted VNS can provide durable benefit in some TRD populations

Evidence position. Long-term observational/systematic evidence.

Confidence. Moderate.

Boundary condition. Delayed onset, invasive device, limited sham-controlled long-term evidence.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 16: taVNS is an established antidepressant treatment

Evidence position. Meta-analytic signal but evidence quality low/very low.

Confidence. Low-to-moderate.

Boundary condition. Heterogeneous stimulation and control conditions.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 17: Precisely timed pairing of VNS with behavior can drive task-specific plasticity

Evidence position. Strong translational proof-of-principle in rehabilitation.

Confidence. High for paired-plasticity principle outside psychiatry.

Boundary condition. Psychiatric extrapolation is a hypothesis, not established treatment evidence.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 18: Closed-loop neuromodulation is already an established psychiatric treatment class

Evidence position. No; compelling proof-of-concept, sparse psychiatric trials.

Confidence. Low clinically, high as engineering rationale.

Boundary condition. Biomarker stability, sensing, adaptation and governance remain unresolved.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 19: Reliable psychiatric neural biomarkers for adaptive stimulation are already available

Evidence position. Candidate biomarkers exist; generalizability is weak.

Confidence. Low-to-moderate.

Boundary condition. Within-person signals can be useful without being population-level diagnostic biomarkers.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 20: LIFU/tFUS offers non-invasive access to deeper, more focal targets than conventional surface electrical/magnetic methods

Evidence position. Strong technical/anatomical rationale and growing human physiology evidence.

Confidence. High for technical potential, low-to-moderate for psychiatric efficacy.

Boundary condition. Parameter standardization and long-term safety/efficacy remain under study.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 21: Temporal interference can non-invasively and selectively treat deep psychiatric circuits

Evidence position. Human feasibility emerging; therapeutic psychiatric evidence minimal.

Confidence. Low for clinical efficacy.

Boundary condition. Deep-field distribution and physiological mechanisms remain active research areas.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 22: Pairing stimulation with psychotherapy/learning is necessarily superior to stimulation alone

Evidence position. No universal rule. A 2026 meta-analysis of rTMS + CBT in depression found a small-to-moderate incremental effect over rTMS controls, while other modality/context literatures remain heterogeneous.

Confidence. Moderate for specific rTMS + CBT depression pairing; low-to-moderate as a general cross-modality principle.

Boundary condition. Pairing effects depend on disorder, task, timing, comparator and state; positive evidence in one pairing must not be generalized to all neuromodulation + experience combinations.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mecha-

nism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 23: Memory reactivation + TMS can reliably rewrite pathological memories clinically

Evidence position. Very small systematic evidence base, mainly experimental.

Confidence. Low.

Boundary condition. Reconsolidation boundary conditions are substantial.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 24: An attractor/control framework is a useful synthesis for psychiatric neuromodulation

Evidence position. Increasing computational/network literature supports state-transition and control formulations.

Confidence. Moderate as a model, not as a literal measured clinical entity.

Boundary condition. Brain dynamics are nonlinear, nonstationary and only partially observed; control-energy and basin language are model-dependent.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to move with it.

Claim 25: The Neuromodulatory Accessibility Field is an established scientific quantity

Evidence position. No. It is a Flow Hijacked synthesis built from state dependence, network dynamics, plasticity and control theory.

Confidence. Hypothesis/synthesis.

Boundary condition. Must always be labeled as a conceptual model unless later operationalized and validated.

Interpretive rule. This claim should be used only at the level supported by the evidence above. A mechanistic signal does not become a treatment recommendation merely because it fits the Flow Hijacked model, and a clinical outcome does not validate every proposed intermediate mechanism. The distinction is retained deliberately so that future evidence can strengthen or weaken one layer without forcing the whole framework to

move with it.

Appendix C — Formal Dynamic Lens

The mathematical notation below is intentionally generic. Its purpose is to make hidden assumptions visible, not to claim a fitted whole-brain model. Let $x(t)$ denote the fast neural or network state, $m(t)$ the neuromodulatory and physiological context, $\theta(t)$ slower effective-connectivity and plasticity parameters, $u(t)$ the external intervention and $\xi(t)$ unresolved variability.

$$\mathrm{d}x = F(x;\theta,m)\,\mathrm{d}t + G(x;\theta,m)u(t)\,\mathrm{d}t + \Sigma(x,m)\,\mathrm{d}W_t.$$

$$\mathrm{d}\theta = \varepsilon H(x,\theta,m,u,\text{history})\,\mathrm{d}t, \qquad 0 < \varepsilon \ll 1.$$

The decomposition enforces four distinctions. F describes the intrinsic flow of the current system. G describes how an intervention couples into that system. Σ represents variability and unresolved fluctuations. H describes slower plasticity and metaplasticity through which present activity changes future responsiveness. A treatment can therefore move x acutely while also changing the rule that governs later change.

For a target set Ω and a finite horizon T, a conceptual accessibility can be written as

$$A_T(\Omega \mid x_0, m, \theta, u) = \Pr\{\exists t \le T : x(t) \in \Omega\}.$$

A complementary control-cost expression is

$$E^*(\Omega) = \inf_u \int_0^T \|u(t)\|^2 \, \mathrm{d}t,$$

subject to reaching Ω under the assumed dynamics. These are model-dependent quantities. They must not be described as literal psychological energy or as directly measurable clinical biomarkers without an explicit observation model.

Five intervention routes follow. Neuromodulation may alter F by changing intrinsic flow or effective coupling; alter G by changing responsiveness to input; alter Σ by changing variability or exploration; alter H by changing plasticity rules; or alter effective target geometry because the distributed consequence of a local perturbation depends on network coupling. Each route makes different predictions and should therefore be tested with different measurements.

A crucial guardrail concerns attractor language. In a nonequilibrium, nonlinear, non-normal and partially observed neural system, there may be no single global scalar potential. Basin and barrier language is appropriate when tied to an explicit reduced model or used carefully as shorthand for persistence and transition difficulty. It is not a license to draw a landscape and treat the drawing as the literal brain.

The framework is most useful when it creates prospective comparisons: Does a measured baseline state predict stimulation response? Does a state-triggered policy outperform an open-loop schedule? Does an intervention reduce the dose needed to reach a target network configuration?

Does altered accessibility predict learning from experience after stimulation? Does the system show hysteresis or history-dependent reversal after repeated perturbation? These are questions that can make the synthesis falsifiable.

Appendix D — Cross-Links Across Flow Hi-jacked

Addiction and craving

A high-value learned trajectory can become disproportionately accessible under cue, stress or withdrawal. Neuromodulation matters when it changes the leverage of cues, executive control or learning, but durability also depends on the social and behavioral ecology that follows.

Depression

Future-directed states may remain conceptually imaginable while becoming dynamically difficult to enter. ECT, TMS and VNS provide different forms of evidence that changing system dynamics can reopen action and affective repertoires without identifying one universal depression circuit.

PTSD

Threat states can become rapidly accessible and persistent while safety learning and contextual control remain weak. State dependence and memory reactivation are therefore central, but pairing stimulation with reactivation remains a research question rather than an established rewriting technology.

ADHD

Variability in arousal, gain, salience and control can make cognitive performance highly context-sensitive. The neuromodulation lens emphasizes state regulation rather than a simple deficit in one transmitter.

Psychiatric Drugs and Brain Dynamics

Medication changes $m(t)$ and can also change plasticity rules. Stimulation delivered under a different pharmacological background is not necessarily the same biological intervention.

Body Before Thought

Interoceptive and autonomic state contributes to the initial condition into which cognitive control acts. A bodily shift can therefore precede a change in explanation or explicit belief.

Co Regulation

Another nervous system can alter arousal, prediction and state transitions through social safety, timing and embodied feedback. This is not reducible

to support as a vague psychological variable.

Reconsolidation

Plasticity after retrieval is conditional. Neuromodulation may interact with memory updating only when the relevant destabilization and timing conditions are met.

Existential Re-Orientation

Neuromodulation can increase flexibility and reopen possibility. It cannot determine which possibilities carry meaning. The existential layer supplies orientation where the biological layer supplies renewed capacity for change.

Appendix E — Working Glossary

Accessibility. The modeled ease or probability with which a system can reach a defined state or state set over a specified time horizon.

Adaptive stimulation. Stimulation whose parameters change in response to measured state or feedback.

Arousal. A multidimensional physiological state affecting vigilance, responsiveness and gain; not identical to anxiety.

Attractor. A dynamical concept describing states or sets toward which trajectories converge in a specified model.

BA25 / sgACC. Subgenual anterior cingulate region important in depression circuitry; a network node, not a single depression center.

Biological dose. The effective neural perturbation produced by a device or drug, including anatomy, field, state, timing and history rather than machine settings alone.

Biomarker. A measurable feature associated with a biological or clinical state; predictive use requires prospective generalization.

Closed loop. A feedback architecture in which sensing informs interven-

tion and subsequent measurements update control.

Connectivity targeting. Selecting stimulation sites using functional or structural relationships to a broader circuit.

Control cost. A model-dependent quantity representing the input required to drive a system toward a specified target state.

DBS. Deep brain stimulation through surgically implanted electrodes.

Dynamic functional connectivity. Time-varying statistical dependence among measured brain signals; not automatically causal coupling.

ECT. Electroconvulsive therapy, a controlled seizure treatment with strong efficacy for severe depression.

Effective connectivity. A model of directed influence among neural populations; inference depends on model assumptions.

E/I regulation. Dynamic interaction of excitation and inhibition; not a single global ratio that explains psychiatric disease.

Electric-field modeling. Computational estimation of fields induced by stimulation in individual or template anatomy.

Gain. Sensitivity with which a neural population transforms input into output.

Homeostatic plasticity. Stabilizing adaptations that compensate for sustained changes in activity.

Hysteresis. Dependence of present response on the path or history by which the current state was reached.

iTBS. Intermittent theta-burst stimulation, a patterned TMS protocol used clinically in depression.

LIFU / tFUS. Low-intensity or transcranial focused ultrasound neuromodulation, an emerging non-invasive approach for deep and focal targeting.

Metaplasticity. Change in the propensity for subsequent plasticity as a function of prior activity or stimulation.

Metastability. Temporary stability of neural configurations with ongoing capacity to transition among states.

MST. Magnetic seizure therapy, an investigational seizure-based treatment intended to alter spatial engagement relative to ECT.

Neuromodulation. Change in the conditions under which neural systems respond, couple, learn or transition, rather than simple transmission of content.

Neuromodulatory Accessibility Field. Flow Hijacked conceptual synthesis describing how modulation may change state reachability; not an established biomarker.

Open loop. A protocol delivered without rapid feedback from the current biological state.

Oscillatory phase. Position within a neural rhythm, which can influence excitability and timing of response.

Personalization. Use of individual anatomy, connectivity, physiology, symptoms or biomarkers to select or adjust treatment.

Plasticity. Activity-dependent capacity for durable change in neural function or structure.

Quasipotential. A model-dependent way to characterize transition difficulty in stochastic nonequilibrium systems.

rTMS. Repetitive transcranial magnetic stimulation.

SNT. Stanford neuromodulation therapy, an accelerated, connectivity-targeted iTBS approach studied for depression.

State dependence. Dependence of intervention effect on the system state at the time of perturbation.

tACS. Transcranial alternating-current stimulation, designed to interact with rhythmic neural activity.

taVNS. Transcutaneous auricular vagus nerve stimulation.

tDCS. Transcranial direct-current stimulation, which weakly biases membrane polarization and network excitability.

Temporal interference. Use of intersecting high-frequency electric fields to create a lower-frequency modulation envelope at depth.

tRNS. Transcranial random-noise stimulation.

Tractography. Diffusion-MRI-based reconstruction of probable white-matter pathways; useful but imperfect.

Transition probability. Probability that a system moves from one defined state to another within a specified model and time window.

VNS. Vagus nerve stimulation, usually referring to an implanted device unless specified otherwise.

Appendix F — Anchor Source Register

The entries below are the 76 high-weight anchors selected during Stages 1–8. The descriptive phrase states the role of the source in this monograph; the PMID is the canonical lookup key. The broader screened corpus exceeds 300 records and is deliberately not reproduced here as if every screened paper carried equal evidential weight.

A01. PMID 12031406. cortical neuromodulatory transmitter systems and plasticity. PubMed

A02. PMID 16022602. LC-NE adaptive gain. PubMed

A03. PMID 15944135. uncertainty, neuromodulation and attention. PubMed

A04. PMID 23040816. neuromodulation of brain states. PubMed

A05. PMID 28782684. dynamic network reconfiguration. PubMed

A06. PMID 31076192. neuromodulators and integration/segregation. PubMed

A07. PMID 35594578. homeostatic E/I regulation. PubMed

A08. PMID 35284030. metastable neural dynamics. PubMed

A09. PMID 40103058. mechanisms of metastability. PubMed

A10. PMID 26598772. consensus on homeostatic plasticity with NIBS. PubMed

A11. PMID 24620008. human cortical metaplasticity. PubMed

A12. PMID 40813159. plasticity/metaplasticity with NIBS. PubMed

A13. PMID 26865020. dopamine reward-prediction-error signalling, temporal structure and learning. PubMed

A14. PMID 38876308. serotonergic neuromodulation of synaptic plasticity. PubMed

A15. PMID 32601996. endogenous acetylcholine and cortical microcircuit modulation. PubMed

A16. PMID 39845725. development of brain-network control theory. PubMed

A17. PMID 39075309. network-control pipeline. PubMed

A18. PMID 32905760. brain states and transitions in computational neuroscience. PubMed

A19. PMID 38972502. dynamic functional connectivity in MDD systematic review. PubMed

A20. PMID 42092365. depression as pathological attractor/circuit framework. PubMed

A21. PMID 40999798. neuromodulation and neural networks in psychiatric disorders. PubMed

A22. PMID 41764060. personalizing brain stimulation from circuits to closed-loop control. PubMed

A23. PMID 38040046. rTMS-induced neuroplasticity review. PubMed

A24. PMID 35034759. TMS as a tool for plasticity. PubMed

A25. PMID 18791818. state dependence of TMS. PubMed

A26. PMID 35577959. state-dependent effects of neural stimulation. PubMed

A27. PMID 40194626. personalized vs fixed rTMS targeting meta-analysis. PubMed

A28. PMID 34711062. SNT sham-controlled RCT. PubMed

A29. PMID 41536095. larger SNT replication/EEG study. PubMed

A30. PMID 42508605. accelerated iTBS dose-response meta-analysis. PubMed

A31. PMID 23142067. connectivity-based TMS target logic. PubMed

A32. PMID 40194594. personalized targeting/electric-field modeling. PubMed

A33. PMID 40628558. individualized sgACC connectivity targeting. PubMed

A34. PMID 33243615. TMS expert safety guidelines. PubMed

A35. PMID 41498282. tDCS depression IPD meta-analysis. PubMed

A36. PMID 39211537. tACS neuropsychiatric systematic review. PubMed

A37. PMID 41582468. tRNS psychiatry systematic review. PubMed

A38. PMID 40925398. human temporal-interference systematic review. PubMed

A39. PMID 42157014. deep-brain temporal interference in humans review. PubMed

A40. PMID 40222573. ECT neuroplasticity scoping review. PubMed

A41. PMID 37962811. ECT mechanisms review. PubMed

A42. PMID 40994837. neuroplastic changes across nonpharmacological depression treatments. PubMed

A43. PMID 39714318. ECT PET/SPECT scoping review. PubMed

A44. PMID 42389389. MST vs ECT systematic review/meta-analysis. PubMed

A45. PMID 41176476. long-term cognitive/dementia safety synthesis. PubMed

A46. PMID 39197490. DBS for TRD systematic review/meta-analysis. PubMed

A47. PMID 40579425. sham-controlled OCD DBS IPD meta-analysis. PubMed

A48. PMID 39237552. DBS for substance-use disorders systematic review. PubMed

A49. PMID 34608328. personalized closed-loop stimulation in TRD, proof-of-concept case. PubMed

A50. PMID 38037329. tractography in TRD DBS review. PubMed

A51. PMID 38679323. DBS tractography individual-participant/meta-analytic evidence. PubMed

A52. PMID 40903613. adaptive circuit targeting framework. PubMed

A53. PMID 41093090. intracranial biomarkers for closed-loop psychi-

atric neuromodulation. PubMed

A54. PMID 36936612. functional-network targets in TRD. PubMed

A55. PMID 34400379. connectomic DBS in TRD. PubMed

A56. PMID 37230264. taVNS depression meta-analysis. PubMed

A57. PMID 41106630. long-term implanted VNS in TRD review. PubMed

A58. PMID 24309259. targeted plasticity with VNS. PubMed

A59. PMID 26671658. paired VNS rehabilitation/plasticity mechanism. PubMed

A60. PMID 39243394. neural substrates of paired VNS plasticity. PubMed

A61. PMID 41711827. focused-ultrasound psychiatry scoping review. PubMed

A62. PMID 38645585. human LIFU review. PubMed

A63. PMID 39217636. psychiatric FUS systematic review. PubMed

A64. PMID 39798597. NAcc LIFU OUD pilot. PubMed

A65. PMID 38061596. LIFU safety systematic review. PubMed

A66. PMID 39084519. clinical recommendations for ultrasound neuromodulation. PubMed

A67. PMID 38359933. pharmacological modulation of TMS plasticity systematic review. PubMed

A68. PMID 41526004. multiscale plasticity/ketamine framework. PubMed

A69. PMID 37316665. psychedelics and reopening of social-reward critical period (preclinical mechanistic anchor). PubMed

A70. PMID 40353492. set/setting systematic review. PubMed

A71. PMID 37128856. ketamine + psychotherapy systematic review. PubMed

A72. PMID 42524058. rTMS + CBT for depression systematic review/meta-analysis. PubMed

A73. PMID 42536010. TMS with memory reactivation/reconsolidation systematic review. PubMed

A74. PMID 39094317. PTSD neuromodulation network meta-analysis. PubMed

A75. PMID 40863235. neuroethics of DBS/neuromodulation scoping review. PubMed

A76. PMID 40781164. ethics of closed-loop neuromodulation scoping review. PubMed

Closing Note

The central argument can be stated in one sentence: neuromodulation changes the conditions under which a nervous system can move and learn. That sentence is intentionally broader than any one device and narrower than a claim of mind control. It places magnetic, electrical, acoustic, implanted and endogenous modulation inside the same dynamic problem while preserving the different evidence levels of each technology.

The next stage is not expansion for its own sake. It is audit: checking that every strong sentence is matched to evidence of the right type, that negative and mixed trials are represented fairly, that safety language is current, and that the novel Flow Hijacked model remains visibly separated from established clinical knowledge. Only after that audit should the monograph be treated as publication-ready evidence architecture for the public site and ASK.