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NEWSLETTER

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Neurotherapeutics and Brain Health Intelligence Brief

This month, we step back from the device and approval landscape to address a foundational question: *Why do the most serious neurological conditions resist pharmacological solutions that have transformed other fields of medicine?*

The answer is not a failure of chemistry or effort. It is biology. Conditions like Alzheimer's disease, treatment-resistant depression, and TBI are disorders of neural circuit organization and circuit-level pathology ultimately requires circuit-level intervention. This issue makes that case, examines where the clinical evidence stands, and identifies the biological gaps that will define which neuromodulation programs succeed over the next decade.

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The Limits of the Molecule: Why Complex Neurological Conditions Demand a Different Approach

The most transformative advances in modern medicine have shared a common logic: find the right target, build the right molecule, change the course of the disease.

Nowhere has this delivered more dramatically than in oncology. The identification of BCR-ABL in chronic myeloid leukemia, HER2 in breast cancer, EGFR and BRAF mutations in lung cancer transformed previously fatal diagnoses into manageable or curable conditions. The target is real, the molecule reaches it, the tumor regresses.

Brain disorders present a fundamentally different challenge.

In neurological and psychiatric disease, we have achieved only moderate success in identifying equivalently critical molecular targets. Not for lack of effort, the history of CNS drug development is one of the most resource-intensive scientific endeavors of the past half century. The difficulty is biological. Conditions like Alzheimer's disease, treatment-resistant depression, Parkinson's disease, and epilepsy are not driven by discrete molecular events the way oncogenic mutations drive tumor growth. They are the product of distributed dysfunction across multiple neural circuits involving hundreds of cell types, thousands of molecular interactions, and dynamic activity patterns that evolve over years. No single molecular target, however well-validated, is sufficient to normalize that level of complexity.

This is where neuromodulation and brain-computer interfaces enter not as alternatives of last resort, but as conceptually appropriate responses to the biology. Neuronal signaling is electrochemical by nature: chemical signals converted to electrical impulses, converted back to chemical signals across synapses, driving the coordinated circuit activity that underlies every aspect of brain function. Neuromodulation intervenes at the electrical phase of a process the brain already runs natively. It is not imposing something foreign. It is engaging the brain in its own language at the level of circuit activity where, in most serious neurological conditions, the pathology resides.

The therapeutic target is not a protein or a pathway. It is a network state. For conditions defined by network dysfunction, that distinction is the most consequential idea in CNS therapeutics today.

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The clinical evidence is already compelling. The biological understanding is catching up. This issue examines both, and what the gap between them means for the field.

In our previous issue, we examined the emerging landscape of neuromodulation devices, i.e. the machines themselves, from closed-loop stimulation platforms to emerging brain-computer interface systems. Before going deeper into what those devices are doing biologically, the question is not about engineering but biology: why is a circuit-level intervention the right response to conditions that pharmacology has pursued for decades with only partial success?

WHERE THE MOLECULAR MODEL REACHES ITS CEILING

The clearest illustration of pharmacology's limits in neurology is also its most expensive: Alzheimer's disease. The amyloid hypothesis that accumulation of amyloid-beta plaques is the primary driver of disease, and that clearing them would arrest or reverse progression has dominated the field for over two decades and generated more than 200 failed clinical trials. The recent approvals of LequembiÒ (lecanemab-irmb) and KisunlaÔ (donanemab-azbt) have partially rehabilitated the hypothesis: amyloid can be cleared, and clearing it produces modest slowing of cognitive decline in early Alzheimer's disease.

This is not a failure of pharmaceutical execution. The molecules were well-designed, the trials well-conducted. The problem is that amyloid accumulation is one feature of a disease that also involves tau pathology, neuroinflammation, synaptic failure, vascular compromise, and progressive network disintegration. Clearing the plaque does not restore the circuit. The molecule reached its target. The disease continued.

Depression tells a parallel story. Monoamine-based pharmacology targeting serotonin, norepinephrine, and dopamine transporters and receptors has produced genuine therapeutic benefit for a substantial proportion of patients since the 1950s. It has also left approximately one third of patients without adequate response to multiple medication trials. The underlying picture appears to be a prefrontal-limbic circuit dysfunction that monoamine modulation can influence but not normalize.

Parkinson's disease represents a more complex case. Dopamine replacement therapy is one of the most effective symptomatic treatments in neurology. But Parkinson's is not only a dopamine disorder. The disease involves progressive involvement of other systems that levodopa does not address and may in some cases exacerbate. The molecular target was correct for one dimension of a multidimensional disease. The circuit pathology that defines the disease in its full biological scope has required a different kind of intervention.

Traumatic brain injury offers the starkest illustration. Over a hundred neuroprotection trials in TBI have failed not because the targets were wrong in isolation, but because TBI is not a single-mechanism injury. It is a temporally evolving, spatially distributed cascade involving simultaneous dysfunction across molecular, cellular, and circuit levels. The pathology is a process, not a target.

Stroke offers a related but distinct picture. The only pharmacological intervention proven to improve outcomes in acute ischemic stroke, tissue plasminogen activator, works not by neuroprotection but by restoring blood flow. The neuroprotection literature in stroke mirrors that of TBI: hundreds of trials, no successful translation of a molecular strategy. The biology of acute ischemic injury is too rapid, too multifactorial, and too spatially heterogeneous for a single molecular target to intercept meaningfully.

The more consequential opportunity is post-stroke recovery. Stroke-induced deficits in motor function, language, and cognition reflect the loss of specific circuit capacities and, critically, the brain's capacity to reorganize through neuroplasticity. That reorganization is a circuit-level process that neuromodulation can drive and accelerate. The FDA clearance in 2021 of MicroTransponderÒ's VivistimÒ Paired VNSÔ System is a direct clinical validation of this principle: Paired VNSÔ delivered during rehabilitation functions as a therapy amplifier, enhancing the brain's plasticity response to active motor rehearsal rather than acting as a standalone intervention.

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NETWORK DISORDERS REQUIRE NETWORK INTERVENTIONS

What Alzheimer's disease, treatment-resistant depression, Parkinson's disease, TBI, stroke, refractory epilepsy, and chronic pain share beyond their burden and resistance to pharmacological management is that they are fundamentally disorders of neural circuit organization. The pathology is not localized to a molecule or a cell type. It is expressed in the dynamic activity patterns of networks: pathological oscillations, disrupted connectivity, aberrant synchrony, failed inhibition, self-perpetuating network states that outlast the molecular events that initiated them.

Pharmacology reaches this level of organization indirectly. A drug that hits its intended target does so wherever that target is present simultaneously. The molecular precision that makes pharmacology powerful at the target level dissipates almost entirely at the circuit level.

Neuromodulation is matched to the biology in ways that pharmacology, by design, cannot be. Electrical or magnetic stimulation of a defined brain region can directly modulate the activity patterns of the circuits connected to it. The intervention is spatially targeted, temporally controllable, and titratable in real time. It acts at the level of circuit dynamics where the pathology lives. It is entering an existing biological conversation at one of its native registers.

The clinical record reflects this conceptual fit. Deep brain stimulation of the subthalamic nucleus produces motor improvements in Parkinson's disease that levodopa cannot fully replicate. Vagus nerve stimulation reduces seizure frequency in epilepsy patients who have failed multiple antiepileptic drugs. Repetitive transcranial magnetic stimulation is approved for treatment-resistant depression, targeting prefrontal circuits that pharmacology modulates only indirectly. In each case the intervention is not a pharmacological augmentation strategy. It is a different class of therapeutic engagement.

THE BIOLOGICAL GAP AND WHY IT MATTERS COMMERCIALLY

The field is at an important inflection point. Neuromodulation is attracting serious investment and scientific talent, closed-loop and adaptive systems are moving from academic proof-of-concept toward commercial development, and brain-computer interfaces are beginning the transition from research tools to therapeutic platforms. The conceptual case that circuit-level interventions are the appropriate response to circuit-level pathology is increasingly accepted.

What has not kept pace is the biological grounding needed to develop these interventions rigorously. Little is known about how the brain responds to chronic stimulation, how tissue reactions such as gliosis can be mitigated, or how to optimize patient selection through pre-intervention molecular screening. Monitoring frameworks remain almost entirely symptom-based clinical rating scales and patient-reported outcomes measured at quarterly visits with limited capacity to track the underlying biological processes that chronic stimulation is driving at the tissue, circuit, and system level.

This gap is not merely a scientific limitation. It is a commercial and regulatory liability that is currently underappreciated. A program that cannot characterize the biological effects of its own intervention beyond the symptoms it was designed to relieve carries risk in indication expansion, in adaptive system validation, and in regulatory engagement as frameworks evolve. Companies investing in that biological depth now are not just doing better science. They are building a durable competitive advantage.

SignalNeuro Partners Perspective: *The pharmacological model has not failed in CNS disorders, but it can be effective when it targets the right molecule at the right time. After that window, we are dealing with disorders of neural circuit function which create genuine space for neuromodulation and brain-computer interface approaches. The opportunity is significant and the clinical foundation is established. What the field now requires is the biological depth to match its engineering ambition, specifically, mechanistic understanding of what chronic stimulation does to neural tissue, circuits, and systems over time, and biological monitoring tools capable of tracking those effects. Those are the questions that will define which programs succeed in the next decade of neuromodulation development. They are also the questions that SignalNeuro Partners brings to every program we evaluate.*