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Brain Medicine

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Interventional Brain Medicine: Medicine's newest frontier

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A New Journal to Bridge a Disadvantageous Gap

Dysfunction of neural cells, or their destruction, are the cause of most neurologic and psychiatric diseases. Which specific networks are involved determines whether there is a neurologic or psychiatric disease (or both, as in most cases). Advances in neuroscience have blurred the artificial boundaries between psychiatry and neurology and have contributed to the momentum toward a long-awaited convergence of these disciplines. Unified clinical training has been proposed (1), but current training in the US and much of Europe continues to follow the divergent approach established in the 19th century. As a result, neurology and psychiatry operate isolated from each other, without explicit or consistent criteria for why a disorder is claimed by one discipline or the other. Pathologic processes that affect purely "neurologic" or "psychiatric" brain circuits are the exception and are not the rule. This split approach hinders access to the best quality care for patients with brain disorders. A new journal has been created with this in mind (2). *Brain Medicine* will embrace an inclusive way forward that uniquely holds the potential to shift current paradigms (2).

A Model of Convergence: Interventional Brain Medicine

There are several areas where the fields are already converging, such as increased neuroimaging of psychiatric disorders (3) or psychotherapeutic techniques being adopted in neurology clinics (4). But perhaps nowhere is the way forward more apparent than with the rapidly advancing treatment modalities of brain stimulation. Indeed, dialogue from experts at a Brain Stimulation Subspecialty Summit (BRASSS) held in Boston in 2023 emphasized an interest in cross-disciplinary implementation. *Interventional Brain Medicine* emerged as the leading name for a potential new medical subspecialty. This name and approach build on literature and existing clinics implementing 'Interventional Psychiatry' (5, 6) but expands these treatment tools to include modulation of any brain network.

The prospective subspeciality, Interventional Brain Medicine, represents the newest frontier and embodies the aim of the new journal, Brain Medicine, which will include publications of results from therapeutic modulation of neural cells and circuits across the brain. We do not present a comprehensive review of these modalities. However, we will highlight how the science and practice behind *Interventional Brain Medicine* serve as a model for bringing neurology and psychiatry together and how it fits into the concept of Brain Medicine as medicine's next frontier.

Neuromodulation, or brain stimulation, refers to techniques that use waveform energy to directly and therapeutically perturb targeted brain regions and networks. Recent advancements in neuromodulation modalities also offer a novel paradigm for understanding the brain. These modalities use electrical, magnetic, acoustic, or optical energy to perturb specific brain regions and networks. They also allow valuable insights into the causal relationships between the brain and behavior on an individual-subject basis. Neuromodulation techniques also help refine neurobiological models of brain disorders and offer therapeutic benefits to patients who cannot improve with conventional treatments.

Various neuromodulation modalities are available as clinical or investigational approaches for treating neurological and psychiatric conditions. These include open-loop deep brain stimulation (DBS) and responsive neurostimulation (RNS), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES) [which includes transcranial direct current (tDCS), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS)], electroconvulsive therapy (ECT), magnetic seizure therapy (MST), epidural cortical stimulation (ECS), spinal cord stimulation (SCS), transcranial/low-intensity focused ultrasound (tFUS/LIFU), and temporal interference (TI). While some novel approaches have promising evidence, we will focus on those already in clinical use to highlight the trans-disciplinary utility and potential of the tools of the emerging subspecialty of *Interventional Brain Medicine*.

Invasive Modalities

Deep Brain Stimulation

Perhaps the most classical approach to neuromodulation is the direct delivery of electrical stimulation to brain tissue. Deep brain stimulation (DBS) is an invasive technique that involves implanting electrodes in specific brain regions and delivering electrical pulses to modulate activity. Currently, DBS is primarily clinically used for movement disorders, including essential tremor, dystonia, Parkinson's disease (7), and epilepsy (8) and, thus, is most often considered a "neurological" treatment. However, within psychiatry, it also has an FDA humanitarian device exemption for obsessive-compulsive disorder (OCD) (9); although underutilized, it has also shown efficacy in some studies and case series in depression, Tourette syndrome (10), and addiction (11). Unfortunately, the expansion of DBS within brain medicine indications has been limited by availability, cost, and apprehension of an invasive procedure, especially by psychiatrists who are not familiar with DBS (12). Awareness is a particular barrier among psychiatrists owing, in part, to a fragmented field where "neurologic" treatments are not widely considered for psychiatric patients, [although many medications developed initially for classical neurological disorders like epilepsy can also treat depression and mood disorders] (13, 14). The future of DBS involves more precise and personalized circuit-based targeting for a broader range of neurological and psychiatric symptoms, closed-loop paradigms that adjust stimulation parameters based on disease biomarkers, and combination therapies that integrate DBS with pharmacological, behavioral, or cognitive interventions (15). While interest in using DBS across the spectrum of Brain Medicine continues to grow, the benefits from these advancements in clinical practice remain mostly limited to patients with "neurological" disease. Notwithstanding, DBS has the potential to offer powerful and trans-diagnostic alternatives for pervasive symptoms of brain circuit disorders.

Responsive Neurostimulation

Responsive neurostimulation (RNS) also involves implanting electrodes in specific brain regions, but unlike DBS, it delivers stimulation only when abnormal activity is trained and detected in a closed-loop fashion. RNS was approved by the FDA in 2013 for the treatment of focal epilepsy that does not respond to medication or surgery (16). RNS disrupts the synchronization of epileptic neurons to restore normal activity patterns (17). While currently only FDA-cleared for epilepsy, there is research

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underway to expand the indications for other brain medicine disorders, such as Parkinson's disease, essential tremor, and dystonia, and investigate the long-term effects on neural connectivity and plasticity (18, 19). Promisingly, similar systems are also being evaluated for psychiatric diseases using closed-loop stimulation for depression, binge eating disorder, and OCD (17, 20, 21).

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) delivers electrical pulses invasively or noninvasively to the neck or to a branch of the vagus, activating brainstem nuclei and causing widespread neurotransmitter release (22). VNS was initially developed in the 1980s as a treatment for refractory epilepsy (23) but was also found to have antidepressant effects and was FDA-cleared for the treatment of major depressive disorder in 2005 (24, 25). It is predominantly still used for refractory epilepsy. However, the emergence of noninvasive systems has led to evaluation for other neuropsychiatric conditions, such as Alzheimer's disease, post-stroke recovery, post-traumatic stress disorder, autism, and addiction, as well as for enhancing cognitive performance, learning, and memory (26). Despite its relatively low risk, along with regulatory approvals for depression, its adoption in clinical practice for depression remains limited. This is likely due to the lack of a convincing Class 1 evidence clinical trial of efficacy in depression, and at least in part due to provider awareness, access, and training in programming the device. Notwithstanding, it has created some inroads in thinking about the brain holistically, especially in guiding treatment for patients with both epilepsy and prominent mood symptoms. This should serve as a pattern for usage as evidence mounts for its efficacy in addressing specific symptoms of brain circuit disorders.

Noninvasive modalities

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) involves the induction of a brief generalized seizure under anesthesia by applying an electrical current through the scalp. While ECT has been used for over 80 years, it remains the most effective and fast-acting treatment for severe and treatment-resistant depression, as well as other mood disorders, catatonia, and psychosis (27). While not typically used in clinical neurology, ECT does have evidence for safety and efficacy in treating Parkinsonism (28) as well as status epilepticus (29). The future of ECT may involve improving its safety and tolerability, refining electrode placement and stimulation parameters, combining it with other therapies, such as transcranial magnetic stimulation (TMS) and ketamine, and better elucidating its mechanisms of action (30–32). Similarly to other modalities, ECT is almost exclusively used by "one side" of Brain Medicine; most neurologists have very little awareness or comfort with using this potentially life-saving therapy in times of need, such as refractory status epilepticus.

Transcranial Magnetic Stimulation

Modern transcranial magnetic stimulation (TMS) was invented in 1985 and approved for the acute treatment of depression in 2008 (33). It is a noninvasive technique that creates electrical activity in the brain via magnetic waves through an electric coil positioned on the surface of the scalp. Through manipulation of stimulation parameters, it can induce long-term potentiation (LTP) or depression (LTD)-like effects, which are thought to exert a top-down effect from cortical areas through the disease network (34, 35). Innovations since its conception have included more efficient delivery systems, various coil designs to shape the induced field to activate specific brain networks, targeting via neuronavigation, and different protocols to deliver more rapid or effective treatment (36–38). Clinically, TMS is mainly used for FDA-cleared psychiatric indications, including depression, OCD, and smoking cessation. However, single-pulse TMS is also FDA-cleared for migraine, and TMS was just recently cleared for pain.

Further, there is evidence for its use in neurodegenerative diseases, movement disorders, epilepsy, and multiple sclerosis (39). In fact (and case in point to highlight our argument), TMS was originally and exclusively used by motor neurophysiologists (40). But a potentially important moment in the development of TMS as an antidepressant occurred when a dual-trained (neurology and psychiatry) physician (M.S.G., author) was exposed to TMS in a neurology/psychiatry fellowship and "borrowed" this technology for a new area of research and eventually leading to FDA approved indication. With a demonstrated ability to modulate cortical tissue and with a good safety and tolerability profile, it is surprising that TMS has not been adopted for additional indications, especially in neurology. Perhaps too little cross-disciplinary thinking, which the journal *Brain Medicine* aims to address, has limited TMS expansion.

Conclusion

These current FDA-cleared brain stimulation modalities will likely soon be joined by others (e.g., low-intensity focused ultrasound, transcranial direct current stimulation). However, if brain medicine physicians are not exposed to these modalities by cross-disciplinary training, will they be utilized by the "other" specialty (even when FDA-cleared)? How many psychiatrists consider DBS for OCD? How many neurologists consider TMS for migraine? In our experience, the answer is very few. We have highlighted these tools with indications across brain medicine, although they are all dominated by the use of the specialty in which they were first developed. Importantly, this emerging field is just beginning, and many other investigational indications have good evidence and will likely be FDA-cleared. Not all physicians treating brain disorders need to become experts in brain stimulation modalities. However, they need to be aware of these modalities to refer patients who are refractory to treatment or may prefer non-medication treatment approaches. They may be tailored to individual patients and integrated into a comprehensive treatment algorithm for patients with different brain circuit disorders. By increasing the exposure and awareness of different brain stimulation modalities, physicians can genuinely operate with a "full toolbox" for treatment across the spectrum of Brain Medicine. Until we bring these fields together, we are limiting how much we can help patients with novel brain stimulation approaches to brain disease. Indeed, we see *Interventional Brain Medicine*, with its current and rapidly emerging potential for use across disciplines, as a type for other brain subspecialties, where physicians approach diagnostics and treatments without an arbitrary border that inevitably leaves the "other" affected brain cells and circuits underrecognized and undertreated.

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