(Vaish *et al*, 2010), and nucleic acid aptamers. At present, we are using neurochips to identify rare nucleotides isolated from combinatorial libraries consisting of hundreds of billions of candidate sequences based on relative affinities for small-molecule neurotransmitter targets. We have also developed micro- to nanoscale surface patterning techniques (Liao *et al*, 2012) and used high-throughput microfluidics (Liao *et al*, 2013) to create multiplexed neurotransmitter substrates. A significant advantage of multiplexed patterning is the capacity to capture and to sort different neurotransmitter-specific aptamers side-by-side while providing opportunities to determine and to compare *in situ* binding affinities.

The discovery of neurotransmitter aptamers will enable their functional integration into nanometer-diameter field-effect transistor (FET) nanowires, which will function as neurotransmitter recording elements (Figure 1). Devices patterned with aptamer-modified FETs will be used to carry out dynamic *in vivo* monitoring of neurotransmission with response times on the order of milliseconds (or faster) (Kim *et al*, 2015). When combined with appropriate passivation to suppress biofouling, microsensors that detect dopamine with sub-second temporal resolution have been shown to function over months *in vivo* in rats and mice (Clark *et al*, 2010). Thus, neurochips will enable the development of devices that will advance the understanding of the roles of small-molecule neurotransmitters in the complex landscape of brain interneuronal communication and dysfunction. Unraveling the emergent properties of integrated chemical neurotransmission associated with neural circuits using this approach will be advantageous for uncovering processes associated with cognition, emotion, and learning and memory.

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Closing the Loop in Deep Brain Stimulation for Psychiatric Disorders: Lessons from Motor Neural Prosthetics

Deep brain stimulation (DBS) is a promising technique for modulating circuits underlying mental illnesses, but has not done well in clinical trials (Dougherty *et al*, 2015). Advocates have argued that the trial failures arise from a need to better define the anatomic target for stimulation (Riva-Posse *et al*, 2014). This ignores a larger issue: DBS is an open-loop, static therapy. Patients' disorders, on the other hand, are not static. Symptoms change over hours to days, but DBS programming visits occur every 4–12 weeks. To resolve that mismatch, investigators are now pursuing 'closed-loop' DBS, where the device itself monitors patients' brain activity and self-titrates therapy to a desired endpoint (Figure 1). The challenge, however, is determining what to monitor. Verified neural biomarkers for psychiatric disorders remain elusive. Preliminary data suggest candidate markers (Widge *et al*, 2015), but they are far from the real-time algorithms needed for effective feedback-controlled DBS.

A different neuroscience community has had greater success in 'reading out' the brain: brain–computer interface (BCI) researchers. Their technologies 'decode' movement signals from the cortex, then convey movement goals to assistive devices. Closed-loop DBS researchers seek to do something similar, decoding a patient's emotional state. BCI investigators have uncovered two insights that could assist psychiatry's quest. First, encoding matters—decoding is better with a robust model of how cortical regions encode mental states. This matters for psychiatry, because disorders like depression and post-traumatic stress disorder are heterogeneous. Effective decoding may require identification of discrete

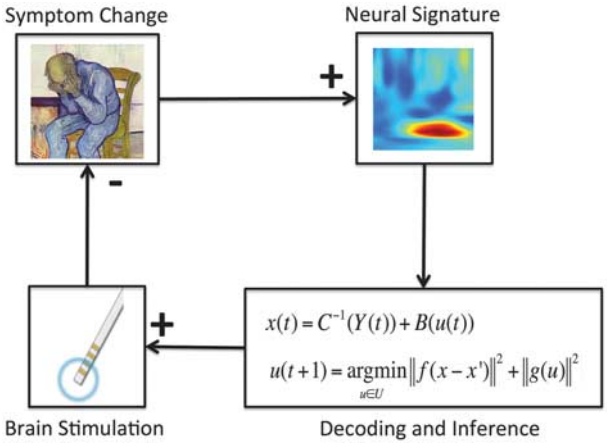

Figure 1. Schematic of closed-loop DBS control. A change in psychiatric symptoms (likely a dimensional construct such as negative mood, over-generalized fear or hyper-arousal) leads to a stereotyped change in neural activity. This is detected by a neural decoding algorithm, which automatically adjusts brain stimulation parameters according to a pre-defined transfer function. The resulting change decreases the symptom level, which stabilizes the system in a homeostatic loop.

circuit-based endophenotypes, analogous to research domain criteria constructs. For instance, preliminary data suggest that DBS response at the ventral striatum target may depend on changes in fronto-cingulate activity evoked by Stroop-like tasks (Widge *et al*, 2015). This cross-diagnostic approach may be broadly useful in dissecting DBS' mechanisms of action.

Second, neural plasticity can help. A recent surprise from BCI studies is that models are helpful, but not always necessary. A motivated subject can learn to skillfully control a prosthetic limb or an internal neurostimulator, even if the mapping between neural firing and device behavior does not match 'natural' input–output relationships. As the user trains with the BCI, the brain re-maps its firing patterns to match the device's control scheme (Moritz and Fetz, 2011). In effect, the decoded patterns become a readout of the user's intention—what he/she wants the device to do at that moment. For a prosthetic limb, this is an instantaneous motion command. For psychiatry, it would be a stimulator command. For instance, one could place a recording electrode in an area that contains emotion-related signals, then link the amplitude of a DBS intervention to the intention-modulated signals in that area. The patient's signals in the recorded area would then 'tune' the DBS intervention as needed. We recently showed that rodents can learn to use prefrontal cortex signals in precisely this fashion to activate DBS-like stimulation (Widge and Moritz, 2014). Similar strategies may be useful for modulating fear behaviors in anxiety disorders, using fronto-limbic networks as targets (Besnard and Sahay, 2015).

DBS remains an interesting technique, and closed-loop approaches may make it more useful for a broader group of patients. Despite recent clinical trial failures, the prospects for psychiatric DBS may be brighter than ever.

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Heteroreceptor Complexes and their Allosteric Receptor–Receptor Interactions as a Novel Biological Principle for Integration of Communication in the CNS: Targets for Drug Development

The receptor–receptor interaction field began with the studies on the