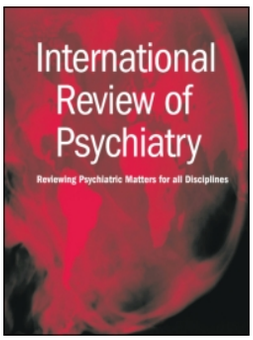

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REVIEW ARTICLE

Closed-loop neuromodulation systems: next-generation treatments for psychiatric illness

Meng-Chen Lo and Alik S. Widge

Department of Psychiatry, Massachusetts General Hospital, Charlestown, MA, USA

ABSTRACT

Despite deep brain stimulation's positive early results in psychiatric disorders, well-designed clinical trials have yielded inconsistent clinical outcomes. One path to more reliable benefit is closed-loop therapy: stimulation that is automatically adjusted by a device or algorithm in response to changes in the patient's electrical brain activity. These interventions may provide more precise and patient-specific treatments. This article first introduces the available closed-loop neuromodulation platforms, which have shown clinical efficacy in epilepsy and strong early results in movement disorders. It discusses the strengths and limitations of these devices in the context of psychiatric illness. It then describes emerging technologies to address these limitations, including pre-clinical developments such as wireless deep neurostimulation and genetically targeted neuromodulation. Finally, ongoing challenges and limitations for closed-loop psychiatric brain stimulation development, most notably the difficulty of identifying meaningful biomarkers for titration, are discussed. This is considered in the recently-released Research Domain Criteria (RDoC) framework, and how neuromodulation and RDoC are jointly very well suited to address the problem of treatment-resistant illness is described.

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Deep brain stimulation; neuromodulation; bioengineering; electrophysiology; transdiagnostic; biomarker

What is a closed-loop neurostimulator?

'Closed loop' refers to any system containing feedback—the ability to sense whether stimulation is having a desired effect, and to adjust stimulation in response to that sensing. In contrast, the psychiatric brain stimulation modalities tested to date in humans are 'open loop'—they deliver energy, but the only readout is in the slow clinical response (or lack thereof). Most steps towards closed-loop systems for psychiatric disorders have focused on invasive electrophysiologic systems—implantable devices that record electrical activity from one or more brain region(s) and deliver electrical stimulation to the same or different brain regions (Figure 1). The detected brain signals from one or more brain regions would be processed by a controller using a real-time algorithm, and the electrical stimulation titrated based on the recorded signals. A simpler version of such a device might be 'human in the loop', where the device does not automatically self-adjust, but clinicians can observe the recorded brain signals and provide manual adjustment of the stimulation (Widge, Arulpragasam, Deckersbach, & Dougherty, 2015). Closed-loop stimulation technology has shown promise as a treatment for various diseases. For example, pain relief can be improved by sensing the patients' body activity and position to adjust spinal cord electrical stimulation using a closed-loop system (The RestoreSensor System, Medtronic, Minneapolis, MN) (Schade, Schultz, Tamayo, Iyer, & Panken, 2011; Schultz et al., 2012). In epilepsy, closed-loop responsive cortical stimulation treatment has shown >40% seizure reduction compared to baseline in a blinded clinical study (NeuroPace, Mountain View, CA) (Heck et al., 2014; Morrell & Halpern, 2016). In Parkinson's disease, closed-loop electrical stimulation has shown improvements in motor response compared to open-loop, continuous stimulation in both primates and humans (Little et al., 2013, 2014; Rosin et al., 2011). This has been demonstrated in acute settings with brief stimulation, but implanted trials are being planned.

The need for closed-loop systems in psychiatry

Given that most other closed-loop successes have involved implanted devices, deep brain stimulation (DBS) may be the most promising option for a closed-loop psychiatric therapy. Open-loop DBS, in

CONTACT Alik S. Widge awidge@partners.org

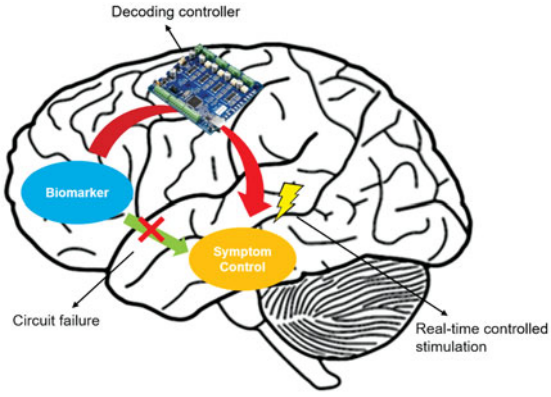

Figure 1. Schematic of one possible closed-loop stimulator realization. The controller system senses ('decodes') electrophysiological biomarkers from a brain region that is associated with disease symptoms. It delivers electrical stimulation to a deep brain structure based on the real-time algorithm.

open-label studies, has caused substantial improvements in patients' symptoms (Malone et al., 2009; Mayberg et al., 2005; Nuttin, Cosyns, Demeulemeester, Gybels, & Meyerson, 1999). Two targets in particular are very well studied: the 'ventral capsule/ventral striatum' (VC/VS) (Greenberg et al., 2010; Okun et al., 2007) and subgenual cingulate gyrus (Cg25) (Lozano, et al., 2012; Lozano et al., 2008; Mayberg et al., 2005; McNeely, Mayberg, Lozano, & Kennedy, 2008). DBS was first tested for refractory obsessive-compulsive disorder (OCD) at the anterior limb of internal capsule, which evolved into VC/VS as the target itself shifted more posteriorly (Greenberg et al., 2010; Nuttin et al., 1999). Early results targeting VC/VS were promising. In an open-label clinical trial with 26 cases, the mean improvement in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score was 38% (from 34 to 21) and clinical response was observed in 72% of the patients (Greenberg et al., 2010). Comorbid depression also improved, with a mean drop of 43% in the Montgomery-Asberg Depression Rating Scale (MADRS). Fifty per cent of patients met depression remission criteria. That study further motivated other groups to implement DBS for major depressive disorder (MDD). Open-label clinical results were positive, with response and remission rates of 53% and 40%, respectively (Bewernick et al., 2010; Bewernick, Kayser, Sturm, & Schlaepfer, 2012). On the other hand, Cg25 was selected as a possible target for psychiatric DBS based on years of neuroimaging studies (Mayberg et al., 2005). The initial open-label clinical study was also positive, with a 43% remission rate after 6 years of patient follow-up (Kennedy et al., 2011; Lozano et al., 2012; Mayberg et al., 2009).

Despite promising open-label clinical evaluations, recent randomized clinical trials showed inconsistent therapeutic outcomes. A well-controlled, randomized clinical trial of DBS targeting VC/VS for MDD (RECLAIM) was terminated early after negative results from the initial cohort of 30 patients (Dougherty et al., 2015). Although not yet formally published, the BROADEN randomized trial at the Cg25 is known to have met a similar fate (Morishita, Fayad, Higuchi, Nestor, & Foote, 2014). Most recently, Bergfeld et al. (2016) conducted a randomized clinical trial of DBS targeting VC/VS with 25 treatment-resistant patients. This trial differed from BROADEN and RECLAIM in that it used an open-label, extended optimization, followed by a randomized DBS discontinuation experiment after the patients reached their stable clinical response. Patients who received active DBS during the randomized crossover phase scored significantly lower on the Hamilton Depression Rating Scale (HAM-D-17) (13.6) than patients who received sham DBS (23.1). Similarly, a study using VC/VS for OCD found separation between active and sham DBS using a blinded cross-over discontinuation design, with a median difference of 12 Y-BOCS points (Luyten, Hendrickx, Raymaekers, Gabriëls, & Nuttin, 2016). The sensitivity of trial outcomes to design highlights the difficulty of successfully programming open-loop DBS with current clinical decision rules. It also highlights the inconsistency of response—60% of the patients in the Bergfeld MDD trial (15/25) and 33% (8/24) in the Luyten OCD trial were non-responders. These inconsistent results across various facilities and studies raise concerns about the wider use of open-loop DBS for psychiatric disorders. Outcomes with less skilled/experienced clinicians will likely be worse. As a result, the only invasive brain stimulation treatment available today in the US market is the open-loop DBS for OCD patients. The treatment holds a Humanitarian Device Exemption from the Food and Drug Administration (FDA), because very few patients meet criteria for the therapy (Garnaat et al., 2014).

The inconsistent results cannot fully be explained by placebo effects, given the two blinded studies. Subtle misplacement of the electrodes has been suggested to play a role (Makris et al., 2015; Riva-Posse et al., 2014). One of the biggest difficulties, however, is a lack of target engagement. DBS dosages are preprogrammed by the physician and adjusted only during infrequent clinical visits, often months apart. For VC/VS and MFB, DBS is titrated by an interviewing process, based on patients' subjective response to

specific stimulation dosages. For studies targeting Cg25, practices vary, but the most experienced group does not adjust the dose or location at all once stimulation starts. In either scenario, there are no physiological measurements or feedback from the brain to verify that the alleged target circuits are being stimulated or changed (Widge & Dougherty, 2015b). This is concerning, given that acute changes in mood do not correlate well to long-term DBS outcomes (Haq et al., 2011; Widge & Dougherty, 2015a; Widge, Licon, et al., 2016).

Closed-loop systems offer a resolution for this programming challenge. Even in treatment-resistant patients with long-lasting illness episodes, the symptom level can vary dramatically within a day. Therapeutic effects might, therefore, be achieved by tightly matching DBS delivery to symptom changes. Biomarker-based stimulation should more directly address patients' clinical needs, increasing their perceived quality-of-life. Finally, closed-loop systems could prevent 'over-treating'. Overly high stimulation dosages can cause adverse side-effects such as hypomania and impulsivity (Greenberg et al., 2010; Haq et al., 2010; Widge, Licon, et al., 2016). Patients have expressed a strong interest in closed-loop therapies for exactly these reasons. Klein et al. (2016) interviewed participants in DBS clinical trials for depression and OCD on their perspectives towards closed-loop systems. Patients reported a general optimism about closed-loop DBS. They were very interested in the possibility of reducing the trial-and-error aspects of existing DBS, and felt that this was one of the most frustrating aspects of open-loop systems. They also recognized that closed-loop systems, with their capacity for continuous brain recording, could provide a more thorough understanding of how neuromodulation works within the brain. The main challenges now facing the field are the need for DBS devices capable of closed-loop operation and a better understanding of the biomarkers that might guide stimulation.

Available and emerging platforms for closed-loop psychiatric DBS

There are two robust hardware platforms currently available that could support closed-loop DBS for psychiatric disorders: Activa PC + S (Medtronic, Minneapolis, MN) (Stanslaski et al., 2012) and the RNS system (NeuroPace, Mountain View, CA) (Morrell, 2011; Morrell et al., 2014). Activa PC + S technology is based on the Activa PC open-loop neurostimulator. The underlying PC (Primary Cell) technology has been approved by FDA and received the CE mark for treatment of Parkinson's disease (PD) and essential tremor (ET). Activa PC + S builds on the PC technology by adding a sensing (+S) component. By default, the recording and stimulating systems are partitioned, such that closed-loop therapies require special firmware available only under an investigational license. Activa PC + S has been used to study both PD and ET in humans and macaques (Herron, Denison, & Chizeck, 2015; Houston, Blumenfeld, Quinn, Brontë-Stewart, & Chizeck, 2015; Khanna et al., 2015; Quinn et al., 2015; Ryapolova-Webb et al., 2014; Swann et al., 2016). With a laptop computer in the loop to provide *ex vivo* closed-loop control, it has shown some efficacy in PD tremor control (Malekmohammadi et al., 2016).

The most attractive advantage of Activa PC + S is its ability to stimulate and record on the same lead, often by delivering monopolar stimulation and recording from the 'flanking' contacts (Quinn et al., 2015). PC + S is designed to address signal contamination from the stimulating artifact from the concurrent sensing and stimulating system design. The high amplitudes (5–10 Volts) of typical DBS are several orders of magnitude higher than the neural signals of interest. It is, therefore, difficult to extract the signals of interest, in both time and frequency domain during neurostimulation, which is exactly what most investigators need. Activa PC + S addressed the challenge systematically with its hardware and software designs (Stanslaski et al., 2009, 2012). First, the device is designed to sense differentially and symmetrically about the stimulating electrodes. The stimulation artifact can then be rejected as a common mode disturbance to minimize sensing signal contamination (Figure 2) (Stanslaski et al., 2009, 2012). Second, the system implements front-end filtering before the signals enter the active circuitry. DBS typically stimulates at high frequency (e.g. 130 Hz). Therefore, a low-pass filter further suppresses the stimulation amplitude to ensure the normal operation range of the input amplifier. Finally, the system has undergone extensive benchtop analysis by its manufacturer. For each stimulation regime, there are known sensing parameters (filtering band, chopping frequency, ADC sampling frequency, etc.) that optimize separation of the stimulation artifacts from the sensed signals or biomarkers.

The PC + S system has been evaluated using a large animal (ovine) model with the lead implanted in the hippocampus and thalamus for responsive epilepsy stimulation (Stypulkowski, Stanslaski, Denison, & Giftakis, 2013). The device was able to record local

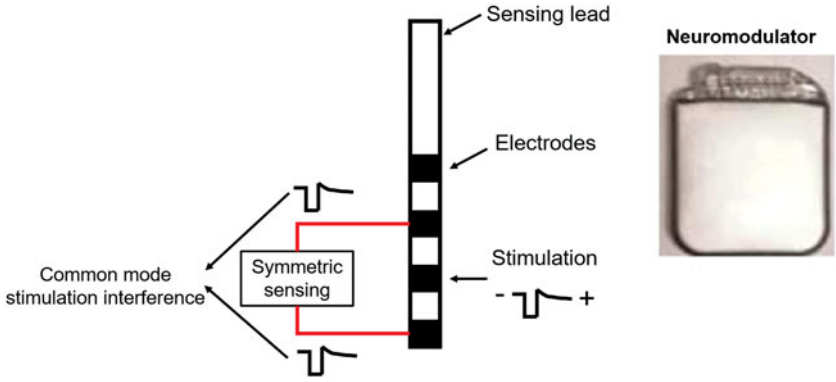

Figure 2. The Activa PC + S electrode sensing configuration. (Left) The sensing electrodes are placed symmetrically about the stimulation electrode. The stimulation interference signals are then recorded as identical signal components (common mode signals) to the amplifier and can be rejected as a common mode disturbance. (Right) The neuromodulation stimulator case is implanted within the patient, enabling monopolar stimulation.

field potentials (LFP) from the hippocampus during thalamic stimulation, and lasted for >1 year with consistent recording capability. This study demonstrated the feasibility, safety, and durability of the closed-loop PC + S system. Similarly, long recording life has been demonstrated in non-human primates, with recordings from both cortex and muscle (Ryapolova-Webb et al., 2014). Importantly, 2 years is the usual battery life of a regular Activa PC implant for psychiatric DBS, implying that PC + S can provide recording and possibly closed-loop therapy over the same duration, and would not require more frequent surgery than the existing technology.

The Activa PC + S system has a CE mark (indicating safety for human use), but has no demonstrated efficacy in any medical condition at this point. It is available in the US, but only as an investigational device for physician-initiated and FDA-reviewed studies. There have been multiple implants in patients with Parkinson disease, with some early findings concerning biomarkers for closed-loop PD therapies (Gmel et al., 2015; Quinn et al., 2015; Swann et al., 2016). Anecdotally, implants of PC + S are ongoing in OCD and MDD patients at both the VC/VS and Cg25 targets. The results of these studies are not yet formally reported, but early conference presentations suggest that changes in the frequency spectrum of the local field potential at either target might be correlated with long-term mood improvement.

The NeuroPace Responsive Neurostimulation System (RNS) is approved by the FDA as a treatment to reduce seizures for patients who are over 18 years old (Sun & Morrell, 2014). The system uses electrocorticographic (EcoG) patterns as a biomarker to trigger brief bursts of brain stimulation. It includes an implantable neurostimulator in the cranium for control, a sensing lead, and a stimulation lead (Figure 3).

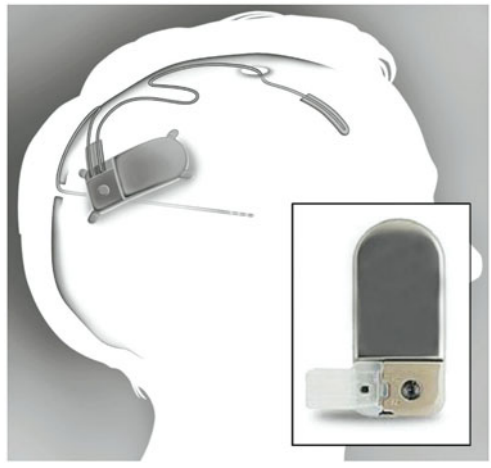

Figure 3. The NeuroPace RNS system. The system includes a neurostimulator, a depth lead for stimulation at or near the seizure foci and a cortical strip lead for EcoG recording (Sun, Morrell, & Wharen, 2008). Reprinted from Sun et al. (2008), copyright (2008), with permission from Springer.

Either lead may be a cortical strip lead or DBS-like depth lead, depending on the location of the patient's seizure focus. The system has four electrodes per cortical strip lead and the depth lead. The neurostimulator continuously monitors brain activity, records signal surrounding each detection or stimulation event, and stores the data for the physician to review. The physician intermittently evaluates the device performance and adjusts the sensing and stimulation parameters if needed. Unlike PC + S, RNS comes with several built-in signal processing algorithms and is configured by default for closed-loop control.

The RNS system incorporates several detection tools for different ECoG patterns (Figure 4) including Half-Wave (Gotman, 1982), Line Length (Esteller, Echauz, Tcheng, Litt, & Pless, 2001), and the Area algorithm (Litt et al., 1999). The Half-Wave method

detects rhythmic activity occurring in a specific frequency range. The detected signals represent the amplitude and frequency component of the electrographic signals. Line Length measures changes in both amplitude and frequency of the signals. The Area algorithm identifies energy changes of the signal, regardless of the signal frequency. The various detection methods provide sensitive and accurate characteristics of brain activity including oscillation changes, LFP spikes, and the combination of those patterns. The RNS system has been approved by FDA as a treatment for epilepsy. It has been tested in Tourette syndrome, which is closely related to OCD, with some promising early results (Okun et al., 2013).

Table 1 summarizes some of the advantages and disadvantages of the Activa PC + S and RNS systems. The most distinctive difference between the two systems is the relative cost of stimulation vs recording. Both devices are battery-powered, with no rechargeable option. The RNS system's battery life is ~3.9 years, but this assumes very intermittent stimulation. If used to deliver stimulation for most of a day, similar to current psychiatric DBS practice, its expected life would be less than a year. Activa PC + S is estimated, with typical DBS-like use, to last ~2 years. The difference between the two systems is the mode that leads to rapid depletion. RNS is optimized for recording, and rapidly loses battery charge when stimulation is used heavily. PC + S is optimized for constant stimulation, and uses battery quickly when frequent recordings and/or telemetry are used. Each is conceivably very useful for closed-loop applications, but requires a careful consideration of design tradeoffs that will limit any potential study.

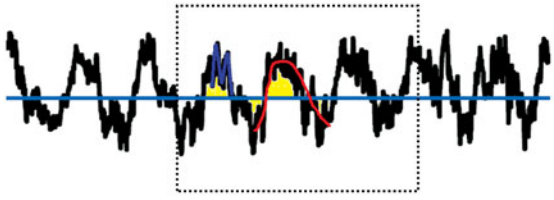

Figure 4. The RNS detection methods. Red: Half-Wave method. The algorithm detects pre-defined segments of the signals partitioned at local and maximum values. The amplitude and duration of the half wave represent the amplitude and frequency of the signals. Blue: Line-Length method. The algorithm calculates the averaged amplitude difference between samples within a short-term window. The value is compared with a long-term window average and detection occurs when the short-term value crosses a certain threshold pre-defined and based on the long-term window average. Yellow: Area method. The algorithm calculates the averaged area underneath the curve of the signal within a short-term window. Detection occurs when the short-term window value crosses the threshold defined by the long-term window averaged area.

Next-generation technologies under development

Improved closed-loop electrophysiologic systems

Both PC + S and RNS represented major technical advances over the prior generation of pure open-loop, non-sensing systems. However, as just described, they also have major limitations, including battery life, channel count, and limited algorithmic sophistication. A general trend in basic neuroscience is the use of increasing channel counts, into the hundreds or even thousands, for sensing and possibly for stimulation. More information can be collected and processed, which in the clinical arena might provide more precise treatments. However, there is a trade-off between the number of electrodes that can be incorporated within the system and power consumption or device packaging. More information extracted from the brain costs more power to analyse and process, and, therefore, decreases the battery-life. Processing also generates heat, and there are strict safety limits on how much heat a medical device can emit into the surrounding tissue. Finally, the device has to be contained within a small anatomical space, so it is challenging to package increased numbers of

Table 1. Summary of the hardware platforms currently available that could support closed-loop DBS.

Platforms	Advantages	Disadvantages
Activa PC + S	• Recording and stimulation on the same lead • System optimized for stimulation • Suitable for DBS-like use with much longer and frequent stimulation • Easily supports existing clinically effective approaches	• Battery powered • The recording and stimulating systems are partitioned • Rapid battery depletion with frequent recording
Responsive Neurostimulation System (RNS)	• Built-in signal processing algorithms • System configured by default for closed-loop control • System optimized for recording • Suitable for short and intermittent stimulation, such as seizure-preventive stimulation, control of brief symptoms	• Battery powered • Cannot record and stimulate at the same lead • Rapid battery depletion with frequent stimulation

electrodes within such a small space. Safety and durability can be an issue if the device is too big or if very fragile connectors must be used to keep their size small. It is, therefore, desirable to advance the technology to provide more customizable hardware and software, better accommodating different therapeutic applications while maintaining clinical safety and feasibility. For psychiatric indications, in particular, it may be essential to have leads in more than one brain location, or to have sensing leads that bring signals from both hemispheres to a single central processor. Mental illnesses are increasingly seen as network-based disorders, and controlling a network may require having multiple points of signal injection within that network.

One new device currently under investigation is being developed by the TRANSFORM DBS program (Bjune et al., 2015; Wheeler et al., 2015) (Figure 5). The system contains a central hub, multiple satellite processors for digitizing and routing neural activity, a transreceiver, and a base station. The central hub incorporates the centralized processing, power, communications, and stimulus pulse generator. It can connect to up to five satellite systems, each with 64 channels, providing up to 320 channels for stimulation or recording. Perhaps most importantly, the central hub also has a rechargeable battery. Major surgery for battery replacement would occur only every 8–10 years, despite the massive increase in recording capability. The base station communicates with the central hub through a wireless transreceiver. This connection permits battery recharging, reprogramming of the device, and download of recorded signals. It also allows the base station to serve as a companion processor, running more advanced signal processing algorithms to help identify key commands that then download to the hub. Multiple satellites can connect to the central hub, enabling access to multiple neural sites. Each satellite is implanted close to a given brain site to minimize noise for high fidelity signal recording. Each satellite has its own electrode front end, but receives power and communication from the hub. The satellite is in turn designed to connect with microelectrode arrays, grids optimized for the cortical surface, or DBS-style depth probes. This design provides the clinicians and researchers the flexibility to configure many different electrode configurations for recording or stimulation. Finally, the hub uses a rigid-flex design for compact packaging, allowing it to conform to the skull for implantation with minimal invasiveness. At present, this system is still undergoing benchtop and animal testing, but, if successful, it will represent a major step forward in the platforms available for developing closed-loop psychiatric therapies. In particular, this network-scale brain access, available over time as a patient goes about his/her daily activities, should offer an unprecedented window into the biology of mental illness.

New physical modalities of brain stimulation

Atop the currently available closed-loop devices, researchers have been developing next-generation technologies that do not specifically rely on electricity. Optogenetics has attracted attention in recent years as a new neuromodulation approach (Aston-Jones & Deisseroth, 2013; Grosenick, Marshel, & Deisseroth, 2015; Steinberg, Christoffel, Deisseroth, & Malenka, 2015). It is a biological technique to provide precise

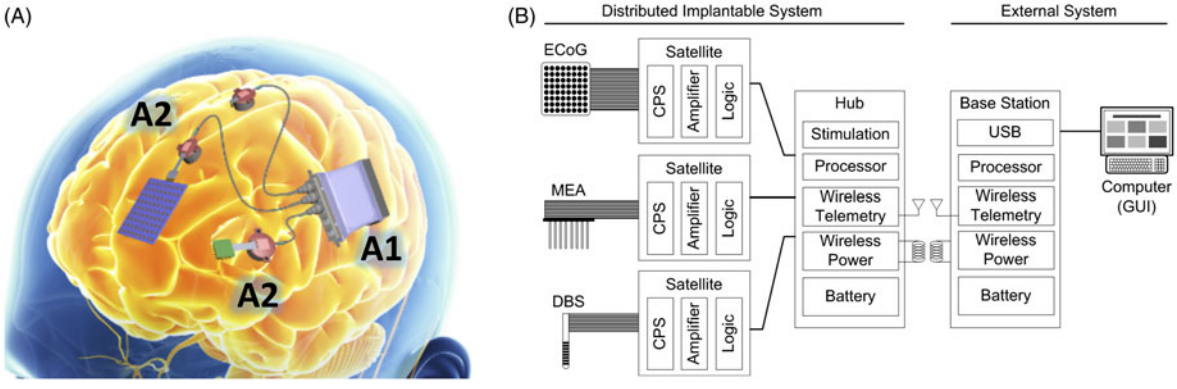

Figure 5. TRANSFORM DBS proposed system. (A) Schematic of cranially mounted device, including the central Hub signal processor and aggregator (A1) and the Satellite systems for signal digitization and stimulation routing (A2). (B) Block diagram of system processing, illustrating partitioning of key components to different aspects of the end-to-end closed-loop therapy (figure courtesy of Draper Laboratory).

control of brain and behaviour through light. The biggest advantage of optogenetics is its precision. Electrical brain stimulation is non-specific, activating many different cell types within a single nucleus. Optogenetics uses genetic tools to introduce non-mammalian ion channels, making specific cells or pathways of interest sensitive to light. Pulses of laser light can then excite or inhibit specifically those cells. This has caused profound behaviour changes in animal models, which might be very powerful if translatable to humans. Creed et al. (2015) showed an example of a translational approach, using both DBS and optogenetics to reverse cocaine-evoked behaviour in mice, through 'optogenetically inspired DBS'. First, they identified a key sub-set of cells that, when genetically targeted and altered by light, abolished drug-seeking behaviour. Second, they combined non-specific electrical stimulation with local blockade of metabotropic glutamate receptors through drug infusion. This caused electrical stimulation to acquire specificity, because it altered local excitability of a key neural population. There remain many translational barriers, and the physics of light scattering are very different in primate brain (Bentley, Chestek, Stacey, & Patil, 2013), but optogenetic techniques continue to revolutionize neuroscience and will almost certainly have an impact on how we develop future DBS systems. As an example of a step towards building optogenetics into a closed-loop technology, Canales et al. (2015) developed a fibre that allows simultaneous optical stimulation, neural recording, and drug delivery channels. These fibres were fabricated from a thermal drawing process that incorporates optical fibre, electrical wires, and microfluidic channels into a single physically integrated neural probe. The system has been validated in mice, and could be scaled up to the dimensions of a human DBS probe with relative ease. This would allow, for example, electrical recording with optical stimulation, completely eliminating the artifact problems that limit existing closed-loop approaches.

Another emerging technology is wireless brain stimulation. This is particularly attractive because it does not require external connections, which may minimize surgical complications or infective risk. It has been theorized that closed-loop DBS might be used to target neuroplasticity, where a relatively short course of treatment could normalize brain circuits by strengthening or weakening target synapses (Widge, Dougherty, & Moritz, 2014). Wireless stimulators would be an excellent option for such treatments, since patients could come to the office for brief treatment courses and otherwise avoid the complications of batteries and wires. This might be a path to achieve the power of DBS with the relative convenience of technologies such as transcranial magnetic stimulation (TMS).

One example is wireless magnetothermal deep brain stimulation. This is a minimally invasive and remote neural stimulation technology that activates heat-sensitive neurons with magnetic particles. When exposed to a rapidly alternating field, the nanoparticles heat up, opening ion channels and causing neurons to fire. This may be a very useful general mechanism, as temperature-sensitive ion channels are found throughout the nervous system (Moran, Xu, & Clapham, 2004). Multiple groups have demonstrated the feasibility of the system using rodent models (Chen, Romero, Christiansen, Mohr, & Anikeeva, 2015; Huang, Delikanli, Zeng, Ferkey, & Pralle, 2010). However, the technology currently lacks a good sensing component and, therefore, requires more investigation before it can be a viable closed-loop neurostimulator. Another example of an emerging wireless technology is neural dust (Figure 6) (Seo, Carmena, Rabaey, Alon, & Maharbiz, 2013). This

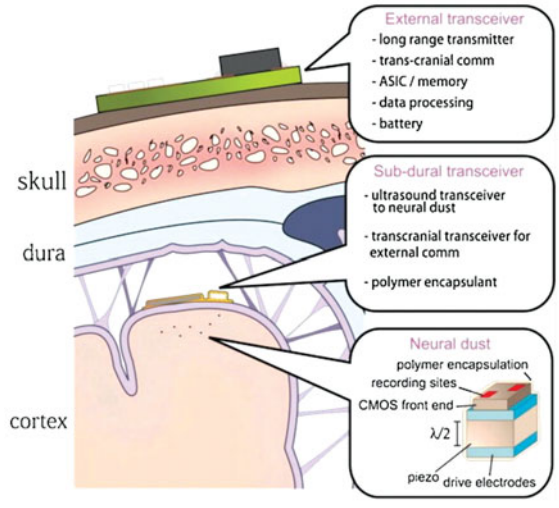

Figure 6. The neural dust system. Dust 'motes' (small recording or stimulating units, ~ 100× smaller than existing electrodes) are implanted within the cortex. A sub-cranial transreceiver is implanted below the dura mater and powered by another external transreceiver through radio frequency (RF) power transfer. The sub-cranial transreceiver couples ultrasound energy into tissue to interrogate each sensing node and deliver stimulation through targeted activating nodes (Seo, Carmena, Rabaey, Maharbiz, & Alon, 2015). In other variants of this system concept, the implanted transreceiver is eliminated and the dust motes are activated/interrogated entirely from outside the skull, for a true minimally invasive system. Reprinted from Seo et al. (2015), copyright (2015), with permission from Elsevier.

system enables recording and stimulation with two technologies: (1) thousands of 10–100 µm free-floating and independent sensor nodes that can detect and report electrophysiological data through ultrasonic backscattering and (2) a sub-cranial ultrasonic transreceiver to power and communicate with the neural dust. Each dust 'mote' is also a piezoelectric antenna that can be made to deliver electrical stimulation when pulsed with a different ultrasonic regime. The system is promising not only because it is wireless, but because it can in theory access thousands of independent channels. There are substantial questions of heat, power, and feasibility to solve, but the massive amount of data obtainable through neural dust could be very beneficial to help decipher the signals of mental illness.

Ongoing challenges and limitations of closed-loop approaches to psychiatric disorders

Despite the available and emerging closed-loop devices for psychiatric disorders, many challenges still remain. The biggest of these is biomarker selection. As previously described, closed-loop technology provides clinicians and researchers the ability to modulate treatment in real time in response to changes in an electrical disease biomarker. However, in psychiatric disorders, there are currently no electrophysiological signals identified that can reliably track patients' overall condition or specific symptoms (Widge, Deckersbach, et al., 2016). It is not yet clear how a pathological state can be differentiated from a healthy state. Progress has been made in 'affective decoding' to generally classify emotions, but there are reasons to believe that this healthy-volunteer research will not work well in clinical populations (Widge et al., 2014). Furthermore, psychiatric diagnoses are highly heterogeneous and likely contain multiple neurological entities. The same clinical phenotype might arise from very different brain pathologies (Cuthbert & Insel, 2013; Insel & Wang, 2010). As a result, while methods such as quantitative electroencephalography have identified candidate markers of treatment response, these have generally not been successfully replicated by independent teams (Mcloughlin, Makeig, & Tsuang, 2014; Widge, Avery, & Zarkowski, 2013; Widge, Zorowitz, et al., 2015). Much work will be needed to identify suitable biomarkers that can be sensed and controlled.

Several strategies have been proposed towards this aim. First, leaders in the US National Institutes of Health (NIH) have proposed a new framework to study not disorders but cross-diagnostic 'Research Doman Criteria' (RDoC) (Cuthbert & Insel, 2013; Insel & Wang, 2010). RDoC seeks to classify an individual patient's mental illness based on functional problems that give rise to those symptoms instead of the symptom clusters (Regier et al., 2013). Researchers and clinicians are expected to develop assessment for those functional domains, and could then apply neuromodulation to domain-specific symptoms and circuits. This domain-oriented approach might address the diagnostic overlap issue and further help biomarker identification. For example, both post-traumatic stress disorder (PTSD) and MDD patients have a common deficit in emotion regulation, at the intersection of the Negative Valence and Cognitive Control RDoC constructs (RDoC Matrix, 2009). That regulation is linked to brain connectivity between the prefrontal cortex and the amygdala (Milad et al., 2009; Rive et al. 2013; Rougemont-Bücking et al., 2011; Widge, Ellard, et al., 2016). DBS that targets this circuit could relieve emotional dysregulation across disorders. Applying this using sensing technologies (such as PC + S, RNS, or TRANSFORM) might help identify human electrophysiological biomarkers in this specific functional domain. Furthermore, this approach also links between human and the animal research communities. It is difficult to screen psychiatric treatments in animals, as commonly used animal behavioural tests are only partly analogous to human emotion (Widge, Arulpragasam, et al., 2015). RDoC constructs and similar domains are designed to align better to those common laboratory assays. A transdiagnostic approach might, therefore, focus on neurological entities that can be measured in both animals and humans, which might yield new ways to screen for biomarkers.

Another strategy to address the biomarker issue is to explore the possibility of a closed-loop DBS that does not need an explicit biomarker. Our group recently demonstrated platform technology for an alternate approach, where patients directly control the stimulator by thinking about what they want it to do (Widge & Moritz, 2014; Widge et al., 2014). A patient would evaluate whether the current simulation parameters (particularly the intensity of stimulation) match his/her needs, and could then volitionally modulate the stimulation parameters. The proposal is a direct combination of DBS with brain computer interfacing (BCI), a technology where neural activity is used as a volitional control signal for prosthetic devices. In this scenario, there is no need to identify a biomarker for each disorder or transdiagnostic construct, although we would still need stimulation target(s) for each. The

device would utilize patients' fundamental desire to relieve their symptoms. The patient would only receive treatment when they explicitly will it, making this a more personalized treatment compared to more traditional concepts of closed-loop stimulation. In rodent models, we have shown that animals can use this type of intentional control to trigger brain stimulation to the medial forebrain bundle (MFB), a reward centre that is also a DBS target for MDD (Widge & Moritz, 2014). There would be much work to translate such a device to the clinic, including identifying a DBS target and stimulation regime that caused noticeable and immediate symptom relief. The technology, nevertheless, offers a different approach to the challenge of biomarker selection.

The final challenge is data volume, especially from next-generation devices. As closed-loop concepts become more popular, many groups have been developing (Ahrens, Orger, Robson, Li, & Keller, 2013; Bjune et al., 2015; Seo et al., 2013; Wheeler et al., 2015). Using benchtop laboratory systems, terabytes to petabytes of detailed data can already be extracted from the brain. The advance allows both clinicians and neuroscientists to study neural activities from single-neuron level to population level (Cunningham & Yu, 2014). However, challenges arise for the analysis of this large-scale neural activity. 'Big data' require massive computational power and very carefully designed algorithms to extract neuronal signatures for a given hypothesis. Traditional data analysis approaches, which average neural features across trials and smooth over time, often yield results that are difficult to interpret. Information can still be buried within the data or even damped out due to the averaging. On the other hand, high channel counts can raise the risk of false-positive findings if not carefully statistically controlled. They also create power considerations for implantable devices, where this kind of massively parallel processing may not be feasible.

Dimensionality reduction can help address the challenge. These methods extract low-dimensional representations of the high-dimensional data, where certain features are preserved or highlighted (Cunningham & Yu, 2014; Wang, Olson, Ojemann, Rao, & Brunton, 2015; Yuxiao Yang & Shanechi, 2015). The widely used dimensionality reduction methods are principal component analysis (PCA) and factor analysis (FA) (Cunningham & Yu, 2014). PCA converts a set of data using orthogonal transformation to capture the greatest variance in the data and FA preserves variance shared across neurons in low-dimensional space (Churchland et al., 2010). However, PCA is a static model that does not account for temporal dynamics of time-series data, whereas the low-dimensional structure of neural data is likely not constant over time. Brunton, Johnson, Ojemann, and Kutz (2016) recently proposed a new approach, dynamic mode decomposition (DMD), to analyse spatial-temporal patterns of large-scale neural recordings. DMD combines power spectral analysis and PCA, enabling rotation of the low-dimensional PCA such that each vector has its own temporal resolution. Other dimensionality reduction methods with likely applications in neural time series are hidden Markov models (Jones, Fontanini, Sadacca, Miller, & Katz, 2007; Ponce-Alvarez et al. 2012; Seidemann, Meilijson, Abeles, Bergman, & Vaadia, 1996), Gaussian process factor analysis (GPFA) (Luttinen & Ilin, 2009; Yu et al., 2009), and latent linear dynamical systems (LDS) (Paninski et al., 2009; Pfau, Pnevmatikakis, and Paninski, 2013; Smith & Brown, 2003; Yousefi et al., 2015). Those methods each assume that there are underlying unobservable variables that explain the population activity, and apply principled statistical methods to extract the most likely values of those variables over time. Finally, neural data can be non-linear in the high-dimensional space, and linear methods might result in loss of features or skewed data interpretation. Therefore, there also exist non-linear dimensional reduction models, such as locally linear embedding (Broome, Jayaraman, & Laurent, 2006; Brown, Joseph, & Stopfer, 2005; Saha et al., 2013) or Isomap (Jenkins & Matarić, 2004; Tenenbaum, et al., 2000), etc. Each closed-loop problem will require careful consideration of whether one of these methods is necessary or appropriate, but the clinical neuroscientist's toolkit is continuing to grow.

Conclusions

Deep brain stimulation for psychiatric disorders has great promise. Well-designed clinical trials have not yielded a strong enough or consistent enough response rate to justify dissemination of open-loop technologies. Closed-loop devices may be a solution, based on lessons learned from our open-loop experience. In the interim, there is increasing use of open-loop DBS devices with sensing capability, which should enable more precise and patient-specific treatment. Patients are strongly interested in any technology that can reduce the trial-and-error nature of DBS or the amount of time between device implant and their first experience of symptom relief. This helps build a case with funding agencies to move the technology forward. Furthermore, closed-loop approaches

will help tremendously in understanding the underlying biology of psychiatric disorders. Every closed-loop device is also a tool for neuroscience, as it creates and stores detailed snapshots of the patient's brain at resolutions not reachable with any other technology. Still, as described in this article, much work remains before closed-loop devices reach clinical psychiatric use: device design, ethical concerns, biomarker selection, and eventually evidence of clinical effectiveness. That work is actively ongoing and even accelerating, on both clinical and basic engineering fronts. The past 5 years alone have seen the debut of two new devices for chronic implantable human use, evidence that this aspect of neuromodulation is prone for growth. We are already well on our way towards more reliable and effective neuromodulation treatments for psychiatric disorders.

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