HHS Public Access

Author manuscript

J Neurol Neurosurg Psychiatry. Author manuscript; available in PMC 2020 July 07.

Published in final edited form as:

J Neurol Neurosurg Psychiatry. 2018 August ; 89(8): 886–896. doi:10.1136/jnnp-2017-317082.

Charting the road forward in psychiatric neurosurgery: proceedings of the 2016 American Society for Stereotactic and Functional Neurosurgery workshop on neuromodulation for psychiatric disorders

Ausaf A Bari[#1], **Charles B Mikell**[#2], **Aviva Abosch**[3], **Sharona Ben-Haim**[4], **Robert J Buchanan**[5], **Allen W Burton**[6], **Stephen Carcieri**[7], **G Rees Cosgrove**[8], **Pierre-Francois D'Haese**[9], **Zafiris Jeffrey Daskalakis**[10], **Emad N Eskandar**[11], **Jason L Gerrard**[12], **Wayne K Goodman**[13], **Benjamin David Greenberg**[14], **Robert E Gross**[15], **Clement Hamani**[16], **Zelma H T Kiss**[17], **Peter Konrad**[18], **Brian H Kopell**[19], **Lothar Krinke**[20], **Jean-Philippe Langevin**[1], **Andres M Lozano**[16], **Donald Malone**[21], **Helen S Mayberg**[22], **Jonathan P Miller**[23], **Parag G Patil**[24], **DeLea Peichel**[6], **Erika A Petersen**[25], **Ali R Rezai**[26], **R Mark Richardson**[27], **Patricio Riva-Posse**[22], **Tejas Sankar**[28], **Jason M Schwalb**[29], **Helen Blair Simpson**[30], **Konstantin Slavin**[31], **Paul H Stypulkowski**[20], **Tor Tosteson**[32], **Peter Warnke**[33], **Jon T Willie**[15], **Kareem A Zaghloul**[34], **Joseph S Neimat**[35], **Nader Pouratian**[1], **Sameer A Sheth**[36]

[1]Department of Neurosurgery, University of California Los Angeles Medical Center, Los Angeles, California, USA

[2]Department of Neurosurgery, Stony Brook University Hospital, Stony Brook, New York, USA

[3]Department of Neurosurgery, School of Medicine, University of Colorado, Aurora, Colorado, USA

[4]Department of Neurosurgery, University of California San Diego Health, La Jolla, California, USA

[5]Department of Neurosurgery, Seton Brain and Spine Institute, Austin, Texas, USA

[6]Neuromodulation, Movement Disorders, and Pain, St. Jude-Abbott, Plano, Texas, USA

[7]Neuromodulation, Boston Scientific Corp, Marlborough, Massachusetts, USA

[8]Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts, USA

[9]School of Engineering, Vanderbilt University, Nashville, Tennessee, USA

[10]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

[11]Department of Neurosurgery, Albert Einstein College of Medicine, Bronx, NY, USA

[12]Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut, USA

Correspondence to: Dr Sameer A Sheth, Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA; sheth@post.harvard.edu.

Contributors AAB, CBM, JSN, NP and SAS collated the minutes into the final manuscript. All other authors participated in discussions about psychiatric neurosurgery and/or commented on the final manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

[13]Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas, USA

[14]Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, USA

[15]Department of Neurosurgery, Emory University, Atlanta, Georgia, USA

[16]Division of Neurosurgery, University of Toronto, Toronto, Ontario, Canada

[17]Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada

[18]Department of Neurological Surgery, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[19]Department of Neurosurgery, The Mount Sinai Hospital, New York City, New York, USA

[20]Medtronic Neuromodulation, Minneapolis, Minnesota, USA

[21]Department of Psychiatry and Psychology, Center for Neurological Restoration, Cleveland Clinic, Cleveland, Ohio, USA

[22]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia, USA

[23]Department of Neurological Surgery, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

[24]Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan, USA

[25]Department of Neurosurgery, University of Arkansas for Medical Science, Little Rock, Arkansas, USA

[26]Neurological Institute, Ohio State University, Columbus, Ohio, USA

[27]Department of Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

[28]Division of Neurosurgery, University of Alberta, Edmonton, Alberta, Canada

[29]Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan, USA

[30]Department of Psychiatry, Columbia University, NY State Psychiatric Institute, New York, NY

[31]Department of Neurosurgery, University of Illinois College of Medicine, Chicago, Illinois, USA

[32]Departmentof Biomedical Data Science, Geisel School of Medicine, Dartmouth University, Hanover, New Hampshire, USA

[33]Section of Neurosurgery, Department of Surgery, University of Chicago, Chicago, Illinois, USA

[34]Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, Maryland, USA

[35]Department of Neurosurgery, University of Louisville, Louisville, Kentucky, USA

[36]Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA

[#] These authors contributed equally to this work.

Abstract

Objective—Refractory psychiatric disease is a major cause of morbidity and mortality worldwide, and there is a great need for new treatments. In the last decade, investigators piloted novel deep brain stimulation (DBS)-based therapies for depression and obsessive–compulsive disorder (OCD). Results from recent pivotal trials of these therapies, however, did not demonstrate the degree of efficacy expected from previous smaller trials. To discuss next steps, neurosurgeons, neurologists, psychiatrists and representatives from industry convened a workshop sponsored by the American Society for Stereotactic and Functional Neurosurgery in Chicago, Illinois, in June of 2016.

Design—Here we summarise the proceedings of the workshop. Participants discussed a number of issues of importance to the community. First, we discussed how to interpret results from the recent pivotal trials of DBS for OCD and depression. We then reviewed what can be learnt from lesions and closed-loop neurostimulation. Subsequently, representatives from the National Institutes of Health, the Food and Drug Administration and industry discussed their views on neuromodulation for psychiatric disorders. In particular, these third parties discussed their criteria for moving forward with new trials. Finally, we discussed the best way of confirming safety and efficacy of these therapies, including registries and clinical trial design. We close by discussing next steps in the journey to new neuromodulatory therapies for these devastating illnesses.

Conclusion—Interest and motivation remain strong for deep brain stimulation for psychiatric disease. Progress will require coordinated efforts by all stakeholders.

INTRODUCTION

The last decade has seen a surge in interest for neuromodulatory treatments for severe, refractory psychiatric disorders. This should come as no surprise, as stereotactic neurosurgery has its origins in the treatment of psychiatric disorders. The first stereotactic procedure in humans, a medial thalamotomy, was performed by Spiegel and Wycis for ‘emotional reactivity’.[1] Their work was followed by efforts from early pioneers such as Leksell and Talairach, who developed stereotactic ablation procedures for psychiatric indications.[2,3] Since the 1950s, stereotactic neurosurgery expanded to include treatments for pain and movement disorders. The development of deep brain stimulation (DBS) for the treatment of movement disorders by Benabid in the late 1980s ushered in a new era of functional procedures.[4]

The immense success, first of lesions and subsequently of DBS for the treatment of movement disorders, led to the resurgence in interest for psychiatric neurosurgery in the 1990s. Driving this interest, along with the availability of technology such as DBS and improved structural and functional imaging, has been a better understanding of the brain circuitry underlying psychiatric disorders. The development of DBS of the subthalamic nucleus for Parkinson’s disease relied as much on the understanding of basal ganglia circuitry by Alexander and colleagues,[6] as it did on the availability of DBS technology itself. Similarly, the evolution in our understanding of the neurobiological basis of obsessive–compulsive disorder (OCD) and depression should enable the successful application of stereotactic neurosurgical procedures for these indications as well.

DBS for psychiatric disease has shown promise for a number of disorders, but this has largely been limited to open-label studies. The disorder with the longest track record of such studies is OCD. Since its inception in 1999,[7] a multicentre open-label trial in patients with severe OCD[8] demonstrated symptomatic improvement in approximately two-thirds of severe, refractory patients, leading to US Food and Drug Administration (FDA) approval through a humanitarian device exemption (HDE) in 2009. Double-blind sham and crossover trials in Europe have further provided class I evidence for this therapy.[9,10] A National Institutes of Health (NIH)-funded randomised, double-blind, sham-controlled US trial (clinicaltrials.gov, NCT00640133) has recently finished enrolment, and results are anticipated in 2018.

DBS for depression has demonstrated clinical benefit in three brain regions in open-label trials, including the ventral capsule/ventral striatum (VC/VS; the ventral-most portion of the anterior limb of the internal capsule and the VS immediately inferomedial to it),[11–15] the subgenual cingulate (SGC; the region of the cingulate cortex ventral to the genu of the corpus callosum)[16–20] and the superolateral branch of the medial forebrain bundle (sl-MFB; a white matter pathway connecting the ventral tegmental region of the brainstem to the frontal lobe).[21] Two recent double-blind crossover trials have used withdrawal designs to provide further evidence for the potential efficacy of DBS for depression.[15,20]

Stereotactic lesions continue to play an important role in psychiatric neurosurgery as well, and the first randomised, double-blind, sham-controlled trial of stereotactic radiosurgery for OCD recently showed promising results.[22] The study reported a significantly greater reduction in OCD symptom scores in the active versus sham group, even though the absolute difference in response rates between the groups did not reach statistical significance until 2 months after the a priori determined 12-month primary outcome interval.

Finally, neurosurgical studies at more preliminary stages abound for a variety of other psychiatric disorders, including anorexia,[23] post-traumatic stress disorder (PTSD),[24] schizophrenia,[25] self-injurious behaviour in autism,[26] traumatic brain injury[27,28] and many others.

Despite these successes and the notable improvement of many patients within these trials, there have been noteworthy disappointments. Two large, industry-sponsored pivotal trials of DBS for depression were aborted when interim analyses showed a low likelihood of meeting primary endpoints.[29,30] The outcomes of these ‘failed trials’ have caused the field to question fundamental aspects of these therapies, including patient selection, trial design, network targeting, funding and, of course, efficacy itself.

The field of psychiatric neurosurgery, therefore, finds itself at a crossroads. Despite the setbacks of these ‘failed trials’, the clinical burden of psychiatric disease remains acute, and the theoretical rationale for invasive neuromodulation continues to grow, with increased commitment from the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, including the NIH and Defense Advanced Research Projects Agency (DARPA).[31] The functional neurosurgery community is now in a position to reflect on its previous experience. The field faces three major questions: (1) how should future clinical

studies be conducted?, (2) what biomarkers are available in psychiatric disease to objectively track symptoms and measure response? and (3) what role will government and industry play in funding and regulating future studies? These questions guided the discussion between leaders in this field, including neurosurgeons, neurologists, psychiatrists, neuroscientists and representatives from the NIH, FDA and industry during the American Society for Stereotactic and Functional Neurosurgery (ASSFN) Workshop on Neuromodulation for Psychiatric Disease, held in Chicago, on 18 June 2016. The goal of this article is to synthesise the discussions that occurred during this day-long workshop, which was sponsored by the ASSFN and its Psychiatric Neurosurgery Committee.

Review of previous literature in this field is limited to points specifically pertaining to discussion topics. More general reviews of psychiatric neurosurgery are available elsewhere.[53233] This paper is organised in three sections: (1) the current state of knowledge; (2) third-party considerations (industry and regulatory); and (3) future directions. In the existing knowledge section, participants discussed what has been learnt from previous trials, including the historical experience with lesion surgery and promising developments in study design and biomarkers. In the section on third-party considerations, participants discussed how the FDA, NIH and industry are currently approaching DBS for psychiatric disorders. Given the location of the meeting in the USA, the discussion focuses on the regulatory framework in the USA, but the principles and lessons learnt are generalisable to the European Union and other countries. Finally, in the section on future directions, we discuss novel concepts in trial design, biomarkers and the use of registries.

CURRENT STATE OF KNOWLEDGE

Lessons learnt from previous trials

Participants discussed the two major halted randomised controlled trials (RCTs) of DBS for depression: the Reclaim trial targeting the VC/VS region[29] and the BROADEN trial targeting the SGC region. While the results of the Reclaim trial had already been published[29] at the time of this workshop, the BROADEN data were still under review at that time and therefore were not fully available to workshop participants. BROADEN results were published during the review of this manuscript[34] and are included here for the sake of completeness and for the relevance they bear to this discussion.

Reclaim was a randomised, double-blind, sham-controlled, multisite trial of VC/VS DBS for depression sponsored by Medtronic. All subjects were implanted and then randomised (in double-blind fashion) after 4 weeks to either receive stimulation (‘active’) or no stimulation (‘sham’) for 16 weeks. During this blinded phase, medications were kept constant, and stimulation parameter adjustments were tightly regulated. Following the 16-week blinded phase, all patients received active, open-label stimulation. The primary outcome variable was response rate, defined ≥50% Montgomery–Åsberg Depression Rating Scale (MADRS) score reduction.

The trial was designed to enrol 208 patients, based on a power analysis assuming a response rate of 15% in the sham group (placebo effect) and 35% in the active group. After the first 30 patients were implanted (29 of whom completed the blinded phase), the sponsor broke

the blind for an interim analysis. At this point, the response rate was 2/14 (14.3%) in the sham group, which was close to the expected rate, but only 3/15 (20%) in the active group, which was less than the expected rate.[29] During the subsequent open-label phase, the response rate was 6/30 (20%) at 12 months and 7/30 (23.3%) at 24 months. The trial was not powered to detect a difference between active and sham in 30 subjects, but given these interim results, the sponsor terminated the trial.

BROADEN was a randomised, double-blind, sham-controlled, multisite, trial of SGC DBS for depression sponsored by St. Jude Medical (now Abbott).[34] All subjects were implanted and then randomised (double blind, 2:1 active:sham) after 2 weeks to active or sham stimulation for 6 months. During the blinded phase, medication changes were not permitted, and stimulation parameter adjustments were closely controlled using a prescribed algorithm. Following the 6-month blinded phase, all patients received active, open-label stimulation. The primary outcome variable was again response rate, defined this time as a ≥40% reduction in MADRS.

The trial was designed to enroll 201 subjects, based on a power analysis assuming a response rate of 18.5% in the sham group and 40% in the active group. An interim analysis was performed after 90 patients had completed the 6-month blinded phase. At this point, the response rate was 5/30 (17%) in the sham group, which was close to the expected rate, but only 12/60 (20%) in the active group, which was less than the expected rate. An FDA-mandated futility analysis demonstrated a 17% chance of achieving a significant difference between the sham and active groups if the study were to be continued. The a priori cut-off for terminating the study was a futility analysis result of <10% chance of success. Nevertheless, the sponsor decided to terminate the study following the interim analysis. Fong-term open-label follow-up results demonstrated a response rate of 29% at 12 months, 53% at 18 months and 49% at 24 months.[35]

The following were proposed during the workshop as speculative reasons for the results observed in these trials.

1. True lack of efficacy of DBS in the respective target. This possibility must of course be considered first in any treatment study that does not demonstrate a difference between active and sham treatment. It is possible that DBS is ineffective in the management of treatment-resistant depression. Workshop participants could not rule out this possibility but considered it unlikely given observed improvement in several patients and other observations such as acute deterioration after unexpected DBS battery depletion. The latter essentially represents a blinded, randomised discontinuation of therapy. Symptomatic decline in such a situation, as has been observed,[36] suggests that at least some patients do derive efficacy from the therapy. The recent DBS for depression study from the Netherlands mentioned above[37] intentionally used a blinded discontinuation design strategy and demonstrated efficacy of the therapy.

2. Placebo response. This effect is clearly present in DBS for depression, which is not surprising given its prevalence in psychiatric treatment studies.[38] Sham response rates in Reclaim and BROADEN trials were 14% and 17%,

respectively. In addition to a pure placebo response, there may have been an additional beneficial effect from trial-related interactions. The intensive follow-up plan for these studies resulted in frequent and positive interactions between enrolled subjects and psychiatrists as well as engaged and empathetic study coordinators. Thus, subjects in the sham arm may have derived therapeutic benefit simply from this increased exposure to caregivers, in addition to placebo effect itself.

3. Trial design. A number of aspects of trial design were scrutinised by the attendees. As described in detail above, both Reclaim and BROADEN subjects were randomised soon after implantation. Placebo effect from the surgical procedure would certainly still be relevant at the onset of the blinded phase. Furthermore, these blinded phases were short (4–6 months) relative to the 12–24 month period over which responses were observed in previous open-label studies. In addition, both trials placed strict limitations on medication changes and stimulation adjustments. For example, Reclaim did not permit monopolar stimulation[29] and BROADEN did not permit adjustment of frequency or pulse width.[34] The higher response rate in the open-label follow-up period in BROADEN, during which stimulation adjustments were unconstrained, suggests that unaccessed regions of the parameter space may have been important. These factors could certainly have contributed to both high sham response and low active response, thereby decreasing the chance of seeing a difference. Further aspects of trial design are discussed in section 4.2 below.

4. Inappropriate or inadequate measurement tools. It is possible that the employed rating scales did not capture subtle improvements. In a number of instances, subjective improvements were noted by family members or even patients themselves—improvements that were not reflected in scores on the chosen symptom scale. The studies may thus have been asking the wrong questions. As an analogy, if patients undergoing DBS for Parkinson's disease were judged based on response to gait freezing and dysphagia rather than brady-kinesia and rigidity, then that therapy would also have been considered a failure. Another complicating factor is that unlike in movement disorder surgery, stimulation effects are not immediate for psychiatric procedures. When patients are fitted with hearing aids, for instance, hearing gains are not immediate; it takes weeks for the brain to adapt to the newly amplified auditory stimuli.[39] Given the complexity of the brain's response to electrical stimulation, it is not surprising that response to DBS surgery is correspondingly delayed. Thus, the question of appropriate biomarkers is not just a matter of 'what' to look for but also 'when' to measure it, and a sophisticated and nuanced approach needs to be adapted to DBS for psychiatric disorders in planning these trials and analysing outcomes. This possibility emphasises the need for more sensitive or appropriate diagnostic scales and objective biomarkers of response.

5. Patient selection. Depression (for example) is a heterogeneous disorder. The diagnosis requires the presence of five of nine possible major criteria[40]; thus, two patients may carry the same diagnosis with only one overlapping symptom.

Compounding the difficulty, it may be the case that stimulation in different targets has different antidepressant effects. Thus, some patients may be better candidates for SGC stimulation, while others may benefit more from VC/VS DBS. While no head-to-head comparison has been done, it was suggested that patients responding to SGC stimulation are more likely to suffer from psychomotor slowing, while those responding to VC/VS DBS may have primary anhedonia. These impressions reflected expert opinion, as hard data to this regard are not available. A related issue is the lack of clinical 'biomarkers' that can predict response. For example, response to levodopa treatment is a predictor of response to subthalamic nucleus (STN) DBS for Parkinson's disease. Patients who do not show such a response are not candidates for the therapy. For psychiatric disorders, we have no such criteria. Contributions of other psychiatric comorbidities are also common and variable. The importance of this heterogeneity is now better appreciated than it was previously and will need to be considered for future inclusion criteria design.

6. Finally, anatomo-functional targeting may have been sub-optimal. This possibility is particularly relevant in the BROADEN study. While the study was ongoing, the Emory group fine-tuned their targeting approach to this region, using DTI to define critical white matter tracts, as described in prior publications.[41–43] Because the trial was already underway, this accumulating knowledge could not be incorporated to refine targeting within the trial. In a very recent open-label study using this method for prospective targeting, this group showed an improvement from a 41% responder rate with anatomical targeting to a 73% responder rate at 6 months and 82% rate at 12 months using the DTI-based method.[44] The same approach may be applied to other targets that are essentially white matter bundles, including the VC/VS and sl-MFB.

Participants also commented generally that pressure to take results from the initial relatively small open-label studies to a large pivotal RCT resulted in premature initiation of the larger trials. Many of the considerations listed above were known or suspected prior to starting the trials. Future work is clearly needed to understand underlying neurocircuitry, how it differs between patients and how best to measure effects of its modulation before embarking on further time-consuming, expensive trials.

Lessons learnt from lesion surgery for OCD and depression

Stereotactic lesions have been used since the 1950s as treatment for refractory neuropsychiatric disorders. Classically, four distinct lesions have been described: anterior capsulotomy, cingulotomy, subcaudate tractotomy and limbic leucotomy.[5] The contemporary indications for lesion surgery are as broad as those studied using DBS, but most commonly include OCD and depression. Because these procedures simply use US FDA-approved 'tools' (eg, radiofrequency electrode/generator, radiosurgery unit, laser ablation process and high-intensity focused ultrasound unit) to create intracranial lesions, they are typically not subject to the 'investigational' categorisation that labels DBS for any indication outside the approved four (tremor and Parkinson's disease as fully approved, and dystonia and OCD as approved on HDE). However, these procedures are only performed at a

relatively small number of centres in the USA and typically under the supervision of local institutional review boards (IRBs).

There are no head-to-head comparisons of lesions and DBS. Retrospective, predominantly uncontrolled, open-label studies report clinical outcomes of lesion procedures that are comparable with similar open-label DBS studies. A recent report described a 47% full and 22% partial response to cingulotomy and limbic leucotomy for severe OCD.[45] Another comparison of anterior capsulotomy to cingulotomy found a comparable response rate of 54% and 41%, respectively.[46] A recent retrospective comparison of capsulotomy to VC/VS DBS (thus comparing interventions in the same region) found a significant advantage in Yale-Brown Obsessive Compulsive Scale (YBOCS) reduction (51% vs 40%) and remission rate favouring capsulotomy.[47]

Lesions offer a number of potential advantages over DBS. Patients do not have to contend with device-related worries (possibility of infection or breakage and requirement for battery replacements), do not have to be ‘tethered’ for their whole lives to a geographical location near an institution familiar with device programming and do not have to make frequent, indefinite visits to the programming site. They also avoid the possibly stigmatising feeling of having a permanent brain implant and therefore ‘being a cyborg’. In some cases, lesion surgery may be the only alternative for a patient with contraindications to DBS, such as skin picking, thin skin due to comorbid eating disorders and others.

However, lesion surgery is irreversible and less forgiving in terms of target accuracy. Once efficacy and side effect magnitude has reached its steady-state level, little can be done to alter it. New DBS technology is increasingly available, including segmented DBS leads with current steering capability and closed-loop devices capable of adjusting stimulation parameters based on real-time measurements of physiological biomarkers. These capabilities further highlight the difference between the immutability of lesions and adjustability of DBS. Patients, families, caregivers and payers need to be educated about the advantages and disadvantages of lesions and DBS.

The beneficial clinical effect following lesion creation is often not immediate. For example, clinical improvement may not manifest for several months, and often continues to evolve with continued improvement reported years after the initial surgery.[2245] Similarly, gradual improvements are also commonly seen in DBS studies.[4849] Therefore, characterisation of the time-course of response is instrumental in the design of future clinical trials. For example, the primary outcome of a recent doubleblind, sham-controlled RCT of Gamma Knife (GK) capsulotomy for OCD measured at 12 months (the end of the blinded phase) showed 2/8 responders in the active treatment group and 0/8 in the sham group, a difference that was not statistically significant ($P = 0.11$).[22] Two months into the open-label phase (month 14), however, a third patient who had had active treatment became a responder. It is impossible to know whether placebo effect after breaking the blind at 12 months contributed to that subject’s further improvement and threshold crossing into responder status. A fourth patient achieved full response at month 18. It is certainly possible, therefore, that had blinding been maintained and the primary outcome measured a few months later, the difference may have been significant. Thus, in addition to the short-term effects from lesion

generation, long-term social and environmental interactions with the underlying neurobiology may be integral in achieving maximal efficacy.

Lesions can be created using a variety of techniques. While traditional methods include radiofrequency ablation and radiosurgery, laser interstitial thermal therapy (TITT)[50] and high-intensity focused ultrasound (HIFU) have gained popularity in recent years.[51] Tike GK, HIFU is an incisionless procedure. Ongoing and pending clinical trials aim to study the use of HIFU in the treatment of severe OCD.[52] While the goal of HIFU in these trials is to create a permanent lesion, in theory HIFU can also be used for non-lesional neuromodulation. While lesions produced by all of these methods may look radiographically similar on MRI, there may be underlying microscopic physiological differences in mechanism of action, a topic worthy of further investigation.

On the flip side, DBS should not be thought of as a functional lesion. The mechanisms underlying DBS are complex, incompletely understood and may include both stimulation and inhibition of neuronal activity.[5354] While both lesions and DBS appear to have comparable clinical efficacy, underlying differences in mechanism of action may account for differences in time course and qualitative clinical results.

Structural and functional neuroimaging will play a greater role in identifying the most efficacious lesion location in the treatment of psychiatric disorders.[5] Indeed, neuroimaging has revealed a high degree of individual anatomical variability in currently used targets.[55] Unlike DBS, there are no restrictions placed on the postoperative MR imaging of patients with lesions, a fact that should be leveraged to characterise the relationship between lesion location relative to patient-specific structural and/or functional anatomy, as in a recent report.[55] This methodology could then be used to prospectively plan individualised lesions. In addition, neuroimaging may be used for response prediction and in selection of patients who are most likely to respond to surgery.[5657]

Closed-loop approach to neurostimulation for psychiatric disease

Participants discussed combining two relatively new approaches: closed-loop DBS and a novel research platform for targeting functional domains in a transdiagnostic fashion, known as Research Domain Criteria (RDoC), in order to improve clinical outcomes.

Unlike other areas of medicine, psychiatry is unique in that it still classifies and treats disorders based on broad symptom categories, and frequently these symptoms are subjectively reported rather than objectively measured. As a counterexample, cancer treatment has evolved to take into account specific genetic and other biological markers, in order to provide more objective patient-specific and disease-specific targeted therapy. Thus, no oncologist would offer chemotherapy based purely on symptoms alone, let alone subjective self-reports. Over the past several years, the National Institute of Mental Health (NIMH) has developed a framework known as the RDoC project, which applies a multidimensional approach to psychiatric disorders based on more granular behavioural and thought patterns, neurobiology and genetics.[58] Rather than avoiding comorbidity and heterogeneity, this approach is designed to incorporate them and is particularly important given how hard it is to find pure Axis 1 disorders like major depressive disorder and PTSD.

The RDoC paradigm may facilitate objective symptom measurement across functional domains, such as avoidant behaviour, excessively rigid behaviour and so on, that are linked to known circuitry that in turn can be targeted by neuromodulation. We can then plot these symptoms on a multidimensional axis and use specifically designed behavioural tasks to assess the impact of neuromodulation on function in each domain.

In closed-loop DBS, signals are recorded from relevant brain structures and used to control stimulation patterns.[59] In the scheme proposed during the workshop, neuronal signals (spikes, local field potentials or combinations) would be combined with behavioural data obtained using the RDoC classification to create a biomarker (eg, local field potential (LFP) signal or network activity) versus RDoC matrix, which could then be decoded using machine-learning algorithms to generate the appropriate control signals.[60] The use of computational methods including machine-learning algorithms may have a special role in identifying underlying patterns that are not obvious in the data. These signals would then be paired with stimulation of relevant structures to treat RDoC-classified symptoms.

Such approaches will be extremely challenging and require multidisciplinary effort. Although DBS for movement disorders was first introduced 30 years ago, closed-loop approaches are just beginning to show initial promise. Furthermore, our understanding of the circuitry underlying movement disorders is more developed than that for psychiatric disorders. Nevertheless, most participants agreed that this is a high-priority area and that progress in one field will likely help in a synergistic fashion with others. In fact, a circuit design was proposed for a device that could potentially record from and stimulate several brain regions, with on-board logic controls and transcutaneous telemetry capability, all within a form factor that could fit within a 14 mm burr hole.[61] As proof of principle, the first example of closed-loop brain stimulation, responsive neurostimulation for epilepsy, is already in clinical use.[6263] Also discussed was an approach using epilepsy monitoring methods to study neuropsychiatric circuitry in detail with intracranial recordings, in order to accelerate our understanding and development of new therapeutic approaches. There was enthusiasm from NIH representation for grant submissions to the BRAIN Initiative using next-generation approaches such as these.

THIRD-PARTY CONSIDERATIONS

Regulatory considerations

A representative of the US FDA discussed the current approach of the FDA towards implantable devices. Of note, a paper has recently been published detailing this process.[64] He explained that a key regulatory consideration in bringing novel neurosurgical interventions for psychiatric disorders to market is communication with the FDA. The cost of bringing a new medical device to market can be substantial. An advanced understanding of the current FDA process and the potential to rationally adapt the process to psychiatric neurosurgery will result in decreased wasted effort, and eventually, better outcomes for patients.

A major goal of the FDA is to provide access to high-quality, safe and effective medical devices to the public. The FDA defines a medical device as any device that *diagnoses, treats*

or *prevents* a medical condition and whose main mechanism of action does not involve chemical interaction. Examples of medical devices include tongue depressors, clot retrieval devices and DBS electrodes. The FDA classifies devices based on the level of control necessary to assure the safety and effectiveness of the device.[65] The three classes of devices, and the requirements that apply to them, are Class I, II or III, on a scale of increasing regulatory control and potential for risk to the patient or user. In general, Class I devices are exempt from regulatory control (eg, tongue depressors). Class II devices require general and special controls, and Class III devices require additional premarket approval (PMA). A reclassification process is available to apply the appropriate level of regulatory controls[66] for a device type based on the most current information regarding its safety and effectiveness.[67] In general, DBS systems are Class III devices. One regulatory pathway to bring a medical device to market is the 510(k) pathway. A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, in other words, substantially equivalent, to a legally marketed device that is not subject to PMA (21 CFR 807.92(a) (3)).[68]

Principal investigators who would like to study a medical device may do so under an investigational device exemption (IDE). An IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a PMA application or a premarket notification 510(k) submission to the FDA. Clinical studies with devices of significant risk must be approved by FDA and by an IRB before the study can begin. Studies with devices posing a non-significant risk must be approved by an IRB alone before the study can begin.[69] While IDE approval time previously used to take over 400 days, over the past few years, the median time to full IDE approval has been reduced to 30 days. Reviews can focus on a number of issues, such as the appropriateness of the proposed scientific endpoints.

The FDA's determination of safety and efficacy is based on valid scientific evidence.[70] Valid scientific evidence can range from well-controlled investigations to partially controlled trials, well-documented case histories by qualified experts and post-market data. An important consideration in any trial design is assessing safety. To aid with submission of protocols, the FDA also offers guidance in the form of a free presubmission pathway, which provides the opportunity to obtain FDA feedback prior to IDE or marketing submission. By this and other means, investigators are encouraged to engage and contact the FDA early in the process. An understanding of the FDA regulatory process by investigators involved in psychiatric neurosurgery will result in matching of agency and investigator expectations, resulting in a more efficient working relationship.

NIMH priorities relevant to neuromodulation in psychiatry

A representative of the NIMH briefly discussed how the NIMH is approaching neuromodulation for psychiatric indications. She discussed four key aspects of the current thinking: (1) impact on public health, (2) overall treatment goals, (3) challenges and (4) current opportunities.

Mental illness results in a tremendous economic and social burden.[71] It is the single largest risk factor for suicide.[72] As is true of many other neuropsychiatric conditions, refractoriness

to pharmacotherapy is common. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that less than 50% of patients respond to the initial medication, with diminishing returns from additional medications.[73] Despite the availability of an increasing number of FDA-approved medications for depression in recent decades, the suicide rates for men and women in the USA increased from 1999 to 2014, with the largest increase being in middle-aged Caucasian males.[74] The limited effectiveness of current medical management provides an opportunity for DBS or ablative surgery as possible therapeutic alternatives.

The ultimate promise of neuromodulation is a relatively rapid and effective treatment response. We know from the ECT literature that patients can respond rapidly and robustly. For example, following ECT, the majority of patients have complete resolution of suicidal ideation by their second treatment.[75] This potential for rapid antidepressant response has also been reported with other interventions, including ketamine,[76] sleep deprivation[77] and DBS.[21]

A number of questions and challenges must be addressed prior to embracing DBS for psychiatric disorders. These include: (1) which patients should we target?; (2) what components of the illness and domains of function are most likely to respond?; (3) What are the specifics of the methodology?; and (4) how do we measure successful response to treatment? The answers to these questions will inform how we devise future trials.

As discussed previously, the classification and diagnosis of psychiatric disease is still rooted in a symptom-based approach rather than more objective neurobiological criteria. This is a problem for treatment development because the diagnostic system is not aligned with the neurobiological basis of the illness. In contrast, and perhaps ironically, preclinical animal models of psychiatric illness often use more objective biological criteria. For instance, we model depression in rodents with tail suspension and the forced swim test, using objectively measurable behavioural responses as the outcomes. Yet, in clinical trials, we focus on *asking patients* about their thoughts and feelings, with little emphasis on neurobiological biomarkers. Not only is it unclear that the animal models represent valid surrogates of the disease, but leaping from objective measurement to subjective self-reports is a massive epistemological gap.

Another observation made by the working group was that the presence of comorbid mental illness is the norm, rather than the exception, in patients with severe refractory disorders such as those undergoing surgical procedures. Recent clinical trials have sought to attain highly homogenous groups, lacking comorbidity and ideally off medications. However, in reality, these patients are highly heterogeneous, typically take multiple medications and often possess multiple comorbidities. This mismatch motivated the previously mentioned RDoC approach,[58] which seeks to define tractable, objectively measureable behaviours that can be measured and modulated. The RDoC approach focuses on domains of function, such as valence, arousal and cognition, described at increasing levels of organisation, from genes, molecules, circuits, all the way to behaviour and finally self-reported subjective symptoms. RDoC is not a diagnostic categorisation system. Instead, it is a research framework for

studying psychopathology based on dimensions of observable behaviour and neurobiological measures to inform target identification and patient selection.

Fortunately, we have made major strides in both behavioural quantification and in understanding of neurobiological mechanisms. Approaches using resting state functional MRI, direct neuronal recordings, even semantic analysis of language using graph-theoretical methods have shed light on mechanisms that may be targetable.[78] As mobile and wearable technology advances, the hope is to put both brain data and behaviour into computer algorithms to link brain activity with behaviour at the speed of thought as in the BRAIN Initiative projects described earlier.

Another major challenge is the identification of the ideal target and stimulation parameters. Target identification is part of a larger *experimental medicine* approach that the NIMH is using to fund trials going forward. In the past, we have had an issue with uninformative trials falling into the 'Valley of Death'. The point of the experimental medicine paradigm is to avoid these failures, by achieving a few key goals: (1) ensure *target identification*, (2) establish the *optimal stimulation parameters*, (3) show that the intervention causes a quantifiable change in a relevant *brain activity* or *mental process* and (4) correlate this change to a *mechanism of action*. NIMH reviewers will not accept grants proposing therapeutic trials that do not conform to this approach. All four goals have to be met. The point is to design trials that are either successful or *fast to fail*; these trials will therefore be informative about the proposed mechanism, whether the results are positive or negative. Of note, neither of the large DBS depression trials used an experimental medicine approach, thus limiting information that they can provide regarding target engagement validity.

Finally, we discussed the specific opportunity for partnership with industry in the context of funding. Recognising the critical role of industry partners, several NIH BRAIN Initiative funding mechanisms specifically request proposals styled as public–private partnerships. These mechanisms encourage collaborations between academia and industry in tackling these challenging problems.

Role of industry

Representatives from Medtronic, St. Jude (now Abbott) and Boston Scientific were present and discussed industry considerations in these trials. There was a consensus that the pivotal trials were initiated too quickly. The commercial value of being 'first to market' for a new indication, especially one as prevalent as depression or OCD, is extremely powerful. The rapid progress to pivotal trial was also due to the success of initial open-label trials, as well as enthusiasm stemming from the success of DBS for movement disorders. In the latter diseases, the treatment effect was so clear that significance may have been achieved, despite shortcomings of trial design. Furthermore, the endpoints of DBS for movement disorders are highly focused and selective neurological criteria with objective measures such as tremor and rigidity, with the explicit awareness that surgery will not slow down or cure disease progression.

A regulatory difference between drug trials and device trials has been pointed out: drug trials explicitly require a phase 2 dose-finding study. If this step were required of the devices, it is

possible that target refinement and endpoint development might have been conducted in such a way that pivotal trials would have been positive. As it is, we are left to consider next steps that require continued buy-in from industry, after the fact. However, a great deal has been learnt from negative trials, both in terms of disease pathophysiology and the possible mechanisms of treatment effect. Given advances in the understanding of the underlying biology of treatment responses to stimulation-based therapies, it should be possible to design more informative trials. Importantly, these advances should allow us to customise disease-specific approaches to target, endpoint and treatment delivery. With these considerations in mind, trials can be conducted that lead to rapid FDA approval, with engagement from insurance payers and a possibly sceptical public.

Medtronic representatives proposed a short framework for the kind of pilot data that would encourage industry funding of new trials. Significant progress in any one or two of these domains would likely cause industry to be willing to fund new trials. First, is there a *diagnostic test* that could reasonably predict response to DBS? For example, we know that levodopa response predicts response to STN stimulation. An analogous test for mood or other psychiatric disorder surgery would be greatly valuable. Second, is there an *acute intraoperative effect of stimulation*? In OCD, for example, a ‘mirth response’ can indicate engagement of the VC/VS target. A similar effect in mood disorders would help localise the most appropriate target region. Third, *rapid onset* of therapeutic effect would also confirm efficacy. It is understood that effects can be seen 1–2 years after surgery, but in the present economic environment, we need to consider whether late effects will be considered cost-effective by payers. Fourth, the treatment effect needs to show *durability* over time. We need to be able to prove that the treatment is ameliorating diseases that are typically characterised by a fluctuating course. Participants acknowledged that prevention of relapse and durability of treatment is a laudable goal. This goal may be accomplished by increasing our knowledge of the underlying neurobiology and searching for more objective clinical measures of response.

FUTURE DIRECTIONS

The case for registries

Maintaining detailed records of patients’ responses to treatment in nationwide databases or registries, appropriately curated for accuracy and consistency, is an alternative means to clinical trials for evaluating treatment outcomes. Participants explored the relative strengths and weaknesses of clinical trials versus patient registries.

Although clinical trials are preferable to data registries from a purely statistical perspective, they are limited by several factors, many of which are unique to psychiatric neurosurgery. These constraints include ethical considerations, proper blinding, the inherent difficulty of creating sham treatments, patient heterogeneity and achieving sufficient sample size. While DBS does provide the ability to switch between ‘on’ and ‘off’ stimulation states during a trial, an advantage for a within-subjects design, trial design in psychiatric neurosurgery remains challenging.

Due to these limitations of trials, some investigators are advocating for the pooling of data into national or global patient registries. Currently, only a tiny fraction of patients in the USA with movement disorders are enrolled in clinical trials, with the rest of the data stored either in local patient registries or not documented at all. In contrast to trials, registries provide a continuous and exhaustive data repository that can be used for multiple studies and is well suited for exploratory analysis. Challenges with registries include localised data collection, the logistics of sharing data across centres, maintaining Health Insurance Portability and Accountability Act (HIPAA) and other regulatory compliance, long-term management and funding. An ideal registry would be funded by the NIH and would have at least part-time staff to maintain it. Registry participants would be encouraged to use Common Data Elements in study design, as the NIH has provided for studies of traumatic brain injury (TBI) and epilepsy.

An example of a registry programme currently in use is the CranialCloud project out of Vanderbilt. The CranialCloud project uses a distributed cloud-based architecture to support crossinstitutional collaboration on movement disorders surgery. CranialCloud includes a HIPAA-compliant pipeline with several distinct steps: (1) data upload, (2) normalisation to a standard reference space, (3) standard preprocessing and (4) advanced visualisation. There are more than 3000 patients represented in CranialCloud, and it allows for collaboration and use of a vast clinical toolbox by practitioners. A similar pipeline may be helpful in psychiatric neurosurgery. Of note, a German group has created similar tools for reconstruction of electrodes and local functional connectivity, called Tead-DBS and Fead-Connectome, respectively.[79–81] As the field progresses, more of these tools will become available.

Novel approaches to trial design

Participants discussed a number of novel concepts in trial design. The gold standard paradigm is the randomised, double-blind, sham-controlled trial. One of the features of DBS, the ability to turn off stimulation, lends itself well to randomisation. This feature has traditionally been used with blinded, crossover designs. However, RCTs were borrowed from the pharmaceutical world, and it may be that attempts to shoehorn surgical treatments into the constraints imposed by traditional RCTs are fraught with unique challenges. Other problems with the conventional RCT include: (1) difficulties with individualised programming, as most trials called for a strict algorithm that prevented the typical parameter exploration with which clinicians are familiar, and thus perhaps impeded identification of optimal settings, (2) delayed onset of treatment response and (3) behavioural responses/immediate responses such as mirth that unblinded patients to their treatment arm. As discussed in section 2 above, these issues may have contributed to the negative results of larger trials.

Participants discussed a variety of alternative trial designs. These included randomised withdrawal designs,[82] waitlist designs[83] and stepped-wedge designs.[84] Randomised withdrawal designs include a significant period (months to a year) of open-label treatment, allowing time to optimise programming. This period is followed by a withdrawal phase in which patients are assigned to cease or taper stimulation. Timing of cessation may be

randomised within a certain narrow window of time and can occur in a double-blind fashion. Symptomatic regression after cessation of therapy provides high-level evidence of efficacy.

Some objections were noted, including interpretational problems if patients have to be censored for ill effects with treatment discontinuation. In addition, abrupt discontinuation may produce effects noticeable enough to the subject to unblind him/her, thus affecting the integrity of the double-blind process. For example, equipment or battery failures in the VC/VS target have been shown to cause worsening of symptoms,[3648] and dystonia battery failures can lead to marked clinical deterioration.[85] A blinded discontinuation phase was described in one experience with SGC DBS, which did correlate with decrease in mood.[86] Gradual tapering of stimulation may not be noticeable to the subject, however, and may therefore allay the concern of unblinding. In fact, a recent trial from the Netherlands used this approach to successfully demonstrate efficacy of VC/VS DBS for depression.[15] This design may thus be an appropriate model for smaller pilot studies.

Larger trials could benefit from waitlist designs or stepped-wedge designs. The advantage of waitlist-type designs (in which patients get surgery at different times, depending on position on a waitlist), or stepped-wedge designs (in which subjects receive a treatment at different times), is that between-subjects analysis is possible. This is also the case in a theoretical efficacy study in which large groups of people are randomly assigned to active or sham stimulation for long periods of time, and then a between-subjects analysis is conducted (which has never been done in DBS). As the placebo effect in psychiatric neurosurgery is a major factor, it is particularly important that a sham procedures and double blinding be maintained.[87]

A final consideration is the fact that observational data (especially about treatment safety and efficacy) can provide very meaningful information. Unlike drug trials, neuromodulation trials that involve permanent device implantation provide the opportunity for long-term follow-up. As several institutions accrue long-term follow-up data on an increasing number of patients, evidence will accumulate regarding treatment efficacy. Discussions with the FDA regarding national registries that closely monitor long-term data on patients outside of formal trials could be very productive in this field. It is conceivable that the FDA may accept such observational studies as sufficient to judge the safety and efficacy of device-based interventions. Without doubt, however, early discussion with the FDA is strongly encouraged for any such development plans.

CONCLUSION

The stereotactic and functional neurosurgical community views psychiatric neurosurgery with guarded optimism. Several small, open-label trials have demonstrated promising results using both lesions and DBS to treat OCD and depression, with other indications under investigation as well. DBS for OCD was given an HDE by the FDA in 2009, thereby permitting on-label use for this indication.

However, two high-profile trials of DBS for depression did not demonstrate efficacy of this therapy. It would be overly simplistic, however, to label these trials as ‘failed’, implying that

no information was gained from the process of designing, executing and analysing them. Scientific integrity requires us to entertain the possibility that these data demonstrate that DBS for depression is ineffective. However, there are several other possibilities that are at least as likely and would need to be ruled out before accepting that interpretation. In fact, these trials highlighted these possibilities in the form of several critical limitations in our understanding of the neurobiology of psychiatric disorders and how to effectively study and measure patient responses to surgical neuromodulation. In this sense, the trials have certainly not 'failed' to make a meaningful contribution to our efforts. Casting light on these limitations will allow us to make improvements in the future, with more thoughtful trial design, incorporation of more sophisticated appreciation of underlying neurocircuitry and integration of more advanced technology.

Further fuelling this effort is the commitment of US governmental agencies to participating in this challenging effort. Discussions during this workshop demonstrated redoubled interest from the NIH in working with investigators and industry alike to create fundable proposals. The FDA remains open minded and willing to engage in finding creative solutions to these problems. Industry partners continue to participate in this discussion and offer their critical perspective.

There is widespread awareness of the enormous burden imposed by mental illness. Millions of patients worldwide remain refractory to the best evidence-based non-surgical treatments. The stereotactic and functional neurosurgical community maintains a realistic view of the challenging road ahead but at the same time remains committed to searching for solutions to these devastating problems.

Acknowledgments

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AA reports grants from Alpha Omega outside the submitted work. The period of funding was completed prior to publication of this manuscript. AWB reports employment from Abbott during the conduct of the study. SC reports employment from Boston Scientific during the conduct of the study. P-FD reports personal fees from Neurotargeting LLC outside the submitted work. ZJD reports other from Magventure, grants from Brainsway NIMH, Brain Canada, OMHF, CIHR and other from Temerty Family Foundation and Grant Family Foundation outside the submitted work. JLG reports personal fees from Medtronic outside the submitted work. WKG reports grants from NIH, Simons Foundation and Biohaven and other from Medtronic during the conduct of the study. BDG has nothing to disclose. He is supported by VA RR&D Center for Neurorestoration and Neurotechnology, N9228-C, PVAMC. REG is a consultant for Abbott (previously St Jude Medical), Medtronic, MRI Interventions, SanBio, Neuralstem, Monteris, Neuropace and Zimmer-Biomet. He has received grant support from NIH, DARPA, NSF, Michael J Fox, CURE, American Epilepsy Society, Neuropace, Medtronic, SanBio, MRI Interventions and Boston Scientific. CH reports honoraria from St Jude Medical and Medtronic. ZHTK reports grants from Alberta Innovates Health Solutions CRIO grant during the conduct of the study. BHK reports personal fees from Medtronic and Abbott Neuromodulation outside the submitted work. LK reports employment from Medtronic during the conduct of the study. He is currently an employee of Magstim. J-PL has nothing to disclose, except he has a patent US 20120290058 A1 pending. AML reports personal fees from Medtronic, St. Jude, Boston Scientific and other from Functional Neuromodulation outside the submitted work. DM reports grants from Medtronic outside the submitted work. HSM reports grants from Hope for Depression Research Foundation, grants from NIMH, non-financial support from St Jude Medical Inc and Medtronic and other from St Jude Medical Inc outside the submitted work. In addition, she has a patent US2005/0033379A1 licenced to St Jude Medical Inc. DP reports employment from Abbott during the conduct of the study. EAP reports grants and personal fees from Medtronic Inc and St. Jude Neuromodulation (Abbott) and grants and personal fees from Boston Scientific Neuromodulation outside the submitted work. AR reports other from Autonomic Technologies, Inc and other from Neurotechnology Innovations Translator and Neurotechnology Innovations Management outside the submitted work. RMR reports grants from Medtronic, Inc outside the submitted work. PR-P reports personal fees from Johnson & Johnson outside the

submitted work. JMS reports grants from Medtronic and Boston Scientific outside the submitted work. HBS reports royalties from UpToDate, Inc and Cambridge University Press. KS reports and discloses past work as a consultant for device manufacturing companies Medtronic, Abbott (formerly St. Jude Medical), Boston Scientific, Nuvectra, Nevro and Stimwave. PHS reports employment from Medtronic during the conduct of the study. JTW discloses consulting/teaching for Medtronic, Inc, MRI Interventions, Inc and NICO Corporation. JSN reports personal fees from St Jude/Abbott Inc during the conduct of the study. NP reports grants from Medtronic and Abbott, grants and personal fees from BrainLab and Second Sight Medical Products and personal fees from Boston Scientific outside the submitted work. In addition, NP has a patent A Method for Deep Brain Stimulation Targeting issued. SAS reports consulting fees from Boston Scientific and Medtronic.

REFERENCES

1. Spiegel EA, Wycis HT, Marks M, et al. Stereotaxic Apparatus for Operations on the Human Brain. Science 1947;106:349–50. [PubMed: 17777432]
2. Leksell L The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 1951;102:316–9. [PubMed: 14914373]
3. Talairach J, Ruggiero G, Aboulker J, et al. A new method of treatment of inoperable brain tumours by stereotaxic implantation of radioactive gold; a preliminary report. Br J Radiol 1955;28:62–74. [PubMed: 13230448]
4. Benabid AL, Pollak P, Louveau A, et al. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 1987;50:344–6. [PubMed: 3329873]
5. Dyster TG, Mikell CB, Sheth SA. The Co-evolution of Neuroimaging and Psychiatric Neurosurgery. Front Neuroanat 2016;10:510.
6. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–81. [PubMed: 3085570]
7. Nuttin B, Cosyns P, Demeulemeester H, et al. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet 1999;354:1526.
8. Greenberg BD, Gabriels LA, Malone DA, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. Mol Psychiatry 2010;15:64–79. [PubMed: 18490925]
9. Mallet L, Polosan M, Jaafari N, et al. Subthalamic nucleus stimulation in severe obsessive–compulsive disorder. 2009;359:2121–34.
10. Luyten L, Hendrickx S, Raymaekers S, et al. Electrical stimulation in the bed nucleus of the stria terminalis alleviates severe obsessive-compulsive disorder. Mol Psychiatry 2016;21:1272–80. [PubMed: 26303665]
11. Schlaepfer TE, Cohen MX, Frick C, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. Neuropsychopharmacology 2008;33:368–77. [PubMed: 17429407]
12. Malone DA, Dougherty DD, Rezai AR, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. Biol Psychiatry 2009;65:267–75. [PubMed: 18842257]
13. Bewernick BH, Hurlemann R, Matusch A, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry 2010;67:110–6. [PubMed: 19914605]
14. Millet B, Jaafari N, Polosan M, et al. Limbic versus cognitive target for deep brain stimulation in treatment-resistant depression: accumbens more promising than caudate. Eur Neuropsychopharmacol 2014;24:1229–39. [PubMed: 24950819]
15. Bergfeld IO, Mantione M, Hoogendoorn ML, et al. Deep Brain Stimulation of the Ventral Anterior Limb of the Internal Capsule for Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry 2016;73:456–64. [PubMed: 27049915]
16. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45:651–60. [PubMed: 15748841]
17. Lozano AM, Mayberg HS, Giacobbe P, et al. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 2008;64:461–7. [PubMed: 18639234]

18. Ramasubbu R, Anderson S, Haffenden A, et al. Double-blind optimization of subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. J Psychiatry Neurosci 2013;38:325–32. [PubMed: 23527884]
19. Merkl A, Schneider GH, Schönecker T, et al. Antidepressant effects after short-term and chronic stimulation of the subgenual cingulate gyrus in treatment-resistant depression. Exp Neurol 2013;249:160–8. [PubMed: 24012926]
20. Puigdemont D, Portella M, Pérez-Egea R, et al. A randomized double-blind crossover trial of deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: a pilot study of relapse prevention. J Psychiatry Neurosci 2015;40:224–31. [PubMed: 25652752]
21. Schlaepfer TE, Bewernick BH, Kayser S, et al. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry 2013;73:1204–12. [PubMed: 23562618]
22. Lopes AC , Greenberg BD, Canteras MM, et al. Gamma Ventral Capsulotomy for Obsessive-Compulsive Disorder. JAMA Psychiatry 2014;71:1066. [PubMed: 25054836]
23. Lipsman N, Woodside DB, Giacobbe P, et al. Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a phase 1 pilot trial. Lancet 2013;381:1361–70. [PubMed: 23473846]
24. Langevin JP, Koek RJ, Schwartz HN, et al. Deep brain stimulation of the basolateral amygdala for treatment-refractory posttraumatic stress disorder. Biol Psychiatry 2016;79:e82–e84. [PubMed: 26475671]
25. Corripio I, Sarró S, McKenna PJ, et al. Clinical Improvement in a Treatment-Resistant Patient With Schizophrenia Treated With Deep Brain Stimulation. Biol Psychiatry 2016;80:e69–e70. [PubMed: 27113497]
26. Sturm V, Fricke O, Bührle CP, et al. DBS in the basolateral amygdala improves symptoms of autism and related self-injurious behavior: a case report and hypothesis on the pathogenesis of the disorder. Front Hum Neurosci 2012;6:341. [PubMed: 23346052]
27. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 2007;448:600–3. [PubMed: 17671503]
28. Rezai AR, Sederberg PB, Bogner J, et al. Improved function after deep brain stimulation for chronic, severe traumatic brain injury. Neurosurgery 2016;79:204–11. [PubMed: 26702839]
29. Dougherty DD, Rezai AR, Carpenter LL, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry 2015;78:240–8. [PubMed: 25726497]
30. Fins JJ, Kubu CS, Mayberg HS, et al. Being open minded about neuromodulation trials: Finding success in our “failures”. Brain Stimul 2017;10:181–6. [PubMed: 28159536]
31. Insel TR, Landis SC, Collins FS. The NIH BRAIN Initiative. Science 2013;340:687–8. [PubMed: 23661744]
32. Patel SR, Aronson JP, Sheth SA, et al. Lesion procedures in psychiatric neurosurgery. World Neurosurg 2013;80:S31.e9–S31.e16.
33. Lapidus KA, Kopell BH, Ben-Haim S, et al. History of psychosurgery: a psychiatrist’s perspective. World Neurosurg 2013;80:S27.e1–S27.e16.
34. Holtzheimer PE, Husain MM, Lisanby SH, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, shamcontrolled trial. Lancet Psychiatry 2017;4:839–49. [PubMed: 28988904]
35. Morishita T, Fayad SM, Higuchi MA, et al. Deep brain stimulation for treatmentresistant depression: systematic review of clinical outcomes. Neurotherapeutics 2014;11:475–84. [PubMed: 24867326]
36. Vora AK, Ward H, Foote KD, et al. Rebound symptoms following battery depletion in the NIH OCD DBS cohort: clinical and reimbursement issues. Brain Stimul 2012;5:599–604. [PubMed: 22305344]
37. Bergfeld IO, Mantione M, Denys D. A randomized, crossover trial of deep brain stimulation of the ventral anterior limb of the internal capsule in depression. European Neuropsychopharmacology 2016;26:S397–S398.
38. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies f major depression: variable, substantial, and growing. JAMA 2002;287:1840–7. [PubMed: 11939870]

39. Lavie L, Banai K, Karni A, et al. Hearing Aid-Induced Plasticity in the Auditory System of Older Adults: Evidence From Speech Perception. J Speech Lang Hear Res 2015;58:1601–11. [PubMed: 26163676]
40. A merican Psychiatric Publishing, Incorporated. Diagnostic and statistical manual of mental disorders, 2013.
41. Johansen-Berg H, Gutman DA, Behrens TE, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatmentresistant depression. Cereb Cortex 2008;18.
42. Gutman DA, Holtzheimer PE, Behrens TE, et al. A tractography analysis of two deep brain stimulation white matter targets for depression. Biol Psychiatry 2009;65:276–82. [PubMed: 19013554]
43. Riva-Posse P, Choi KS, Holtzheimer PE, et al. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatmentresistant depression. Biol Psychiatry 2014;76:963–9. [PubMed: 24832866]
44. Riva-Posse P, Choi KS, Holtzheimer PE, et al. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. Mol Psychiatry 2017;62:10.
45. Sheth SA, Neal J, Tangherlini F, et al. Limbic system surgery for treatment-refractory obsessive-compulsive disorder: a prospective long-term follow-up of 64 patients. J Neurosurg 2013;118:491–7. [PubMed: 23240700]
46. Brown LT, Mikell CB, Youngerman BE, et al. Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: a systematic review of observational studies. J Neurosurg 2016;124:77–89. [PubMed: 26252455]
47. Pepper J, Hariz M, Zrinzo L. Deep brain stimulation versus anterior capsulotomy for obsessive-compulsive disorder: a review of the literature. J Neurosurg 2015;122:1028–37. [PubMed: 25635480]
48. Kennedy SH, Giacobbe P, Rizvi SJ, et al. Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. Am J Psychiatry 2011;168:502–10. [PubMed: 21285143]
49. Crowell AL, Garlow SJ, Riva-Posse P, et al. Characterizing the therapeutic response to deep brain stimulation for treatment-resistant depression: a single center long-term perspective. Front Integr Neurosci 2015;9:117.
50. Willie JT, Laxpati NG, Drane DL, et al. Real-time magnetic resonance-guided stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. Neurosurgery 2014;74:569–85. [PubMed: 24618797]
51. Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. N Engl J Med 2013;369:640–8. [PubMed: 23944301]
52. Jung HH, Kim SJ, Roh D, et al. Bilateral thermal capsulotomy with MR-guided focused ultrasound for patients with treatment-refractory obsessive-compulsive disorder: a proof-of-concept study. Mol Psychiatry 2015;20:1205–11. [PubMed: 25421403]
53. Anderson T, Hu B, Pittman Q, et al. Mechanisms of deep brain stimulation: an intracellular study in rat thalamus. J Physiol 2004;559:301–13. [PubMed: 15218068]
54. McIntyre CC, Savasta M, Kerkerian-Le Goff L, et al. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol 2004;115:1239–48. [PubMed: 15134690]
55. Banks GP, Mikell CB, Youngerman BE, et al. Neuroanatomical characteristics associated with response to dorsal anterior cingulotomy for obsessive-compulsive disorder. JAMA Psychiatry 2015;72:127. [PubMed: 25536384]
56. Rauch SL, Dougherty DD, Cosgrove GR, et al. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for obsessive compulsive disorder. Biol Psychiatry 2001;50:659–67. [PubMed: 11704072]
57. Dougherty DD, Weiss AP, Cosgrove GR, et al. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. J Neurosurg 2003;99:1010–7. [PubMed: 14705729]

58. Insel T, Cuthbert B, Garvey M, et al. Research Domain Criteria (RDoC): Toward a New Classification Framework for Research on Mental Disorders. Am J Psychiatry 2010;167:748–51. [PubMed: 20595427]
59. Hamilton L, McConley M, Angermueller K, et al. Neural signal processing and closed-loop control algorithm design for an implanted neural recording and stimulation system. Conf Proc IEEE Eng Med Biol Soc 2015;2015:7831–6. [PubMed: 26738107]
60. Deng Xinyi, Faghih RT, Barbieri R, et al. Estimating a dynamic state to relate neural spiking activity to behavioral signals during cognitive tasks. Conf Proc IEEE Eng Med Biol Soc 2015;2015:7808–13. [PubMed: 26738103]
61. Wheeler JJ, Baldwin K, Kindle A, et al. An implantable 64-channel neural interface with reconfigurable recording and stimulation. Conf Proc IEEE Eng Med Biol Soc 2015;2015:7837–40. [PubMed: 26738108]
62. Morrell MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology 2011;77:1295–304. [PubMed: 21917777]
63. Sun FT, Morrell MJ. Closed-loop neurostimulation: the clinical experience. Neurotherapeutics 2014;11:553–63. [PubMed: 24850309]
64. Anderson L, Antkowiak P, Asefa A, et al. FDA Regulation of Neurological and Physical Medicine Devices: Access to Safe and Effective Neurotechnologies for All Americans. Neuron 2016;92:943–8. [PubMed: 27930909]
65. Center for Devices, Health R. Classify your medical device.
66. Center for Devices, Health R. Regulatory controls.
67. Center for Devices, Health R. Classify your medical device - reclassification.
68. Center for Devices, Health R. Premarket notification 510(k).
69. Center for Devices, Health R. Overview of device regulation.
70. CFR - Code of Federal Regulations Title 21.
71. Soni A The Five Most Costly Conditions, 1996 and 2006: estimates for the U.S. civilian noninstitutionalized population: meps.ahrq.gov, 2009 http://www.meps.ahrq.gov/mepsweb/data_files/publications/st248/stat248.pdf (accessed 20 Jul 2017).
72. Qin P, Agerbo E, Mortensen PB. Suicide risk in relation to socioeconomic, demographic, psychiatric, and familial factors: A national register–based study of all suicides in Denmark, 1981–1997. Am J Psychiatry 2003;160:765–72. [PubMed: 12668367]
73. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905–17. [PubMed: 17074942]
74. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. Proc Natl Acad Sci U S A 2015;112:15078–83. [PubMed: 26575631]
75. Kellner CH, Fink M, Knapp R, et al. Relief of expressed suicidal intent by ECT: a consortium for research in ECT study. Am J Psychiatry 2005;162:977–82. [PubMed: 15863801]
76. DiazGranados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 2010;71:1605–11. [PubMed: 20673547]
77. Benedetti F, Riccaboni R, Locatelli C, et al. Rapid treatment response of suicidal symptoms to lithium, sleep deprivation, and light therapy (chronotherapeutics) in drug-resistant bipolar depression. J Clin Psychiatry 2014;75:133–40. [PubMed: 24345382]
78. Mota NB, Vasconcelos NA, Lemos N, et al. Speech graphs provide a quantitative measure of thought disorder in psychosis. PLoS One 2012;7:e34928. [PubMed: 22506057]
79. Horn A, Kühn AA. Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. Neuroimage 2015;107:127–35. [PubMed: 25498389]
80. Horn A A structural group-connectome in standard stereotactic (MNI) space Data Brief 2015;5:292–6. [PubMed: 26543893]

81. Horn A, Kühn AA, Merkl A, et al. Probabilistic conversion of neurosurgical DBS electrode coordinates into MNI space. Neuroimage 2017;150:395–404. [PubMed: 28163141]

82. Kopec JA, Abrahamowicz M, Esdaile JM. Randomized discontinuation trials: utility and efficiency. J Clin Epidemiol 1993;46:959–71. [PubMed: 8263581]

83. Wiebe S, Blume WT, Girvin JP, et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 2001;345:311–8. [PubMed: 11484687]

84. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC Med Res Methodol 2006;6:380.

85. Lumsden DE, Kaminska M, Tustin K, et al. Battery life following pallidal deep brain stimulation (DBS) in children and young people with severe primary and secondary dystonia. Childs Nerv Syst 2012;28:1091–7. [PubMed: 22427261]

86. Holtzheimer PE, Kelley ME, Gross RE, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. Arch Gen Psychiatry 2012;69:150–8. [PubMed: 22213770]

87. Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: Placebo, nocebo, lessebo, and lesion effects. Mov Disord 2016;31:290–8. [PubMed: 26952118]

Key points

- DBS for depression was tested in two major trials, Reclaim RECLAI and BROADEN, neither of which provided support for the efficacy of DBS.
- DBS for depression was tested too early using a randomised sham controlled trial design before there was enough evidence regarding optimal target selection, electrophysiological parameters or disease subtypes.
- Disease heterogeneity and the lack of a symptom-based approach may have been major contributing factors that were overlooked in the trial design and analysis.
- In small and single-centre series, patient-specific imaging and target selection have resulted in better outcomes.
- Lesions are relatively safe and low maintenance and demonstrate efficacy quite comparable with DBS. Because they are permanent and irreversible, however, they must be performed by extremely experienced centres.
- Lesions are currently more amenable than DBS to postoperative imaging, a difference that should be leveraged to understand the underlying pathophysiology of neuropsychiatric disorders and how they change with treatment.
- The RDoC research paradigm and electrophysiological biomarkers may be used to identify control signals for next-generation closed-loop neurostimulation.
- Invasive studies of neuropsychiatric circuitry are likely needed to define and refine symptom-specific control signals.
- The FDA should be contacted early in planning of neurosurgical psychiatric trials.
- Multiple regulatory pathways are available for obtaining marketing approval for a device (PMA, 510K, IDE, HDE and so on).
- ‘Valid scientific evidence’ is the standard for FDA approval, and depending on the proposed use of the device, prior regulatory history, and a number of other factors, it can take many forms, including RCTs, partially controlled trials and well-documented case series, to name a few.
- NIH recognises the high socioeconomic burden of psychiatric disorders and is committed to funding efforts to understand underlying mechanisms and improve targeted therapies.
- The ‘experimental medicine’ approach to trial design is now a required element of how the NIMH scores grants, necessitating focus on target identification, dose–response characterisation and mechanisms of action in devising clinical trial strategy.

- Progression from small, open-label studies of DBS for depression to pivotal RCTs occurred too rapidly, with insufficient time to define critical factors such as patient selection, target identification and engagement and measures of efficacy.
- Industry will be more likely to fund future trials when at least some of the following four advances have been developed: (1) a diagnostic test to identify potential responders; (2) a clear acute effect of stimulation in the OR; (3) identification of a relatively rapid onset of the therapeutic effect; and (4) durability of stimulation effects over time.
- Registries can be a source of clinical data that can potentially be used to guide FDA decision making.
- National registries are becoming increasingly available in movement disorder surgery, and similar trends for psychiatric disorders may be useful.
- RCTs are the gold standard means of demonstrating efficacy, but designing appropriate RCTs for DBS for psychiatric indications remains a challenge.
- Alternative trial designs may include randomised withdrawal, stepped-wedge and waitlist designs.