

## Neuroethics Supplement: Psychiatric Applications for DBS: Using Epistemology to Assess Ethics in Research

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### ABSTRACT

In this paper I argue that considerations arising from the epistemic situation of current research into deep brain stimulation (DBS) as a potential treatment for refractory psychiatric disorders such as obsessive compulsive disorder (OCD) and treatment resistant depression (TRD) give rise to a unique ethical context. In this context, neurosurgeons necessarily play a dual role, as the DBS procedure itself provides both a therapeutic option to these otherwise untreatable patients and should be regarded as a potential contribution to ongoing research. I propose that approaches to this dual role suggested by discussions in research ethics concerning therapeutic misconception and equipoise are inadequate to address the ethical requirements of this dual role. As well, I critique a recent effort by Lipsman et al (2010) to describe ethical criteria for these and similar procedures for failing to fully address the dual role of the neurosurgeon who performs DBS on psychiatric patients today.

**Key words:** deep brain stimulation, psychiatric disorders, therapeutic misconception, equipoise

The appropriate ethical approach to contemporary research into the application of DBS for psychiatric indications is revealed by considering relevant epistemic and ethical values, in relation to one another. The epistemic situation is one that calls for further research; while remarkable improvements have been seen among certain patient groups treated with DBS, there is little proven theory to explain these results and a need for confirmation through repetition and control. Ethically speaking, these patients are being treated with DBS because other treatments have failed to relieve them of their suffering; the primary purpose of applying DBS for psychiatric conditions has been and continues to be therapeutic concern.<sup>1</sup> I argue in this paper the key to assessing when and how it is ethical to treat psychiatric patients with DBS lies in considering the epistemic situation at hand in light of the ethical framework in which the practice is already being prescribed. The approach that arises accommodates the dual role that practitioners who treat patients with novel technologies or in a novel fashion must play, for the dual purposes of research and therapy.

### Why current standards for ethical research do not apply.

Current standards for ethical research require that the research produce valid and significant results in terms of safety and efficacy, and that research subjects be protected from exploitation. The requirement that results be valid and significant is usually met methodologically, by reliance on the accepted model of the randomized controlled trial (RCT). An RCT may take place over multiple phases; for example, Phase I research includes trials that apply technologies for the first time in human subjects, and focus on testing both for safety and for confirmation of the effects predicted in pre-clinical animal and laboratory studies. Phase II trials focus on efficacy, establishing within a clinical context that the treatment under study is better than the currently accepted standard of care and that its effects are reliable as well as safe.<sup>2</sup>

Research into DBS as a treatment for OCD and TRD currently lies at the intersection of basic science and translational research: procedures must be valued for their potential to contribute to foundational knowledge as well as toward the refinement of future procedures (Mian, 2010). It is different than Phase I trials under the RCT format in so far as the application of these procedures is not yet grounded by proven theory about mechanisms or disorder etiology: while brain imaging and the refinement of stereotactic surgical technique has allowed for increased accuracy at the front end of these procedures, it remains necessary to perform the procedure itself to gain the necessary data to design a protocol. There is still basic science to be done.<sup>3</sup>

Researchers are at the stage where consolidation among techniques is needed in order for individual trials to create quantitative evidence that can be compared or combined (Lakhan & Calloway, 2010).<sup>4</sup> The thought that DBS is a potential treatment for OCD and TRD came about mainly as a result of observations of psychiatric effects made when applying the procedure to other patient groups, such as those with pain or movement disorders (Mian, 2010; Lakhan & Calloway, 2010). Since the late 1990s, patients with refractory OCD have been given DBS and currently DBS as a treatment for TRD is gaining in popularity; small studies are now being performed around the world, in which individual patients or small groups of patients across surgical centres are regarded as research subjects. In order to move from a situation of serendipity

to one of evidence-based medicine, efforts toward knowledge synthesis must be and are being prioritized so that observations made of individual trials can be aggregated (Lipsman et al, 2010). Synthesis allows for better resource allocation; there are difficulties with providing DBS on a grand scale, with both attaining and justifying funding, as the procedure is costly, invasive and applies to a limited number of patients. Further, synthesis often produces statistically significant results more effectively than repetition (Ionnidis, 2001). Thus, researchers should continue to make use of evidence already available and also, importantly, aim to produce results that better enable synthesis now and in the future.<sup>5</sup>

Phase II RCT research allows for control, by testing upon subjects within a particular patient group, and for generalization, by testing large numbers of subjects in order to limit the influence of confounding factors on results. In contrast, the group of psychiatric patients for whom DBS may work is limited in size and spread across varying circumstances, making it difficult to generalize among them or to account for confounding factors. Factors that contribute to diversion across applications include differences in criteria for patient selection, for example in regard to thresholds for treatment resistance (Bell, 2011) and differences in trial protocol or methodology between centers (Lipsman et al, 2010). The patients themselves have diverse histories, having undergone multiple treatments already, and often suffer comorbid conditions. Thus, they present as a heterogeneous group.<sup>6</sup>

Current theories arising out of DBS research offer further complexity within patient groups, rather than more certainty about accepted patient categories. Depression is increasingly regarded as a system-based disorder; this seems to be confirmed by the fact that a variety of DBS placement options produce similar results in terms of symptom relief (Abosch & Cosgrove, 2008). This holds also for OCD, as current research suggests an underlying complexity to the disorder not yet understood (Mian, 2010). Neurosurgeons interpret the results of DBS in a way that differs from psychiatric categories generally used in patient selection, focussing on clusters of symptoms that respond empirically to particular manipulations of the brain, rather than general effects of the treatment on the disorder suffered as a whole (Bell, 2011). Better patient selection requires a refinement of diagnostic categories to correspond with the theoretical framework used to design an effective treatment, but developing such a theoretical framework requires more research into the relationship between treatment effectiveness and patient categories. Small-scale and individual trials such as have been and continue to be done must carry on with the aim of synthesis in mind before large-scale trials with homogeneous subject groups can even be designed.

Thus, it is incompatible with the current epistemic situation to demand that research into the application of DBS as a treatment for refractory psychiatric disorders adapt to the research standards of contemporary models of evidence-based medicine which prioritize the methods of large-scale RCTs.

### **Why some general approaches to research ethics do not apply.**

DBS is recommended to refractory psychiatric patients principally in order to relieve them of suffering when other methods have

failed. Thus, the primary concern of the surgeon is the individual patient, rather than the results of the surgery or the data it can contribute. The neurosurgeon justifies performing the surgery by appealing to the need to relieve this patient from her suffering, and not (primarily) for the contribution it might make to scientific knowledge. So the neurosurgeon must and does take a therapeutic stance toward both the patient and the procedure itself. What is needed to enable the much-needed research and synthesis of knowledge in this area, however, is that our therapeutic surgeon also take the stance of a researcher, when performing DBS on psychiatric patients.

This neurosurgeon who must regard his work from both the research and therapeutic stances is faced with the dilemma presented by therapeutic misconception. He cannot regard his patient from both perspectives simultaneously: he cannot be expected to prioritize the needs of the patient when taking the stance of the researcher or, when in the therapeutic stance, to stick to pre-determined protocol when his patient's well-being is at stake. From the patient's perspective, she cannot be misled to believe that she is being treated for her condition when research is the primary focus, because the treatment may not be effective, or she may be part of the control population (Miller & Brody, 2003). In order to ensure informed consent, then, the surgeon must play a singular role, so that the patient or research subject has certainty regarding what kind of care and results she can expect; a surgeon who plays both roles toward a patient will encourage therapeutic misconception, rather than prevent it.

This is indeed a problem – the neurosurgeon both ought and ought not play a dual role in regard to the patient-subject and procedures, when it comes to performing DBS to treat refractory psychiatric indications. Research ethics approaches that insist on a sharp distinction between the context of research and therapy do not offer a resolution to this problem. The nature of DBS precludes this: component analysis (Weijer & Miller, 2004), for example, would only reinforce the fact that the application and investigation of relevant theory are inseparable. Furthermore, the small numbers in the target population require that patients be regarded as subjects when possible – and, their vulnerability requires that subjects be primarily considered in light of their status as patients (Lipsman et al, 2010).

A second, closely related concept from research ethics should be considered: equipoise, or whether the relevant community of practitioners agrees overall that a treatment is effective for a patient group, or that further research needs to be done (Freedman, 1997). Because it is generally believed that DBS may have therapeutic value for these otherwise treatment resistant patients, individual clinicians have equipoise on whether or not DBS should be administered. They lack equipoise, however, when it come to the details of the procedure itself, such as the best location for stimulation, the best way to tailor patient care, or the ideal parameters for continuing care, all still matters for debate (Bell, 2011). Thus, they have empirical justification to administer the treatment for therapeutic reasons, as it is reasonably probable that the patient's suffering will be relieved. However, there are epistemic reasons to view the procedure as a means for improving knowledge about how and for whom the treatment best applies (Mian, 2010; Bell, 2011). Individual neurosurgeons both have and lack equipoise in every case; if we use equipoise to examine

this situation, the appropriate ethical stance such a neurosurgeon must take becomes difficult to surmise.

### How to resolve the dual role problem.

One reason for recommending that patients be treated like subjects is if we also hold the aim to limit the amount of time for which this approach is necessary. That is, attaining the maximum amount of knowledge possible from each case should minimize the number of cases required before conclusions can be drawn. Thus, there is an ethical reason for regarding even the compassionate application of DBS as at least a potential research protocol, and for neurosurgeons who perform DBS on these patients to regard themselves as fulfilling a dual role. The epistemic reasons for doing so have ethical implications, as well. For example, in order to tailor procedures to individual patients, more needs to be learned about the relationship between symptom clusters and stimulation locations (Bell, 2011, Lakhan & Calloway, 2010). Empirical research is required; thus DBS must be performed on human subjects. Rather than eliminating or reconciling two disparate contexts, in the case of DBS applications in psychiatry, it is better to see research and therapy as overlapping aspects of a singular application of novel technology. Similarly, rather than eliminating one or reconciling the two roles the neurosurgeon finds herself fulfilling, I argue the duality of treating both patient and subject presents her with a singular ethical context.

Lipsman, Bernstein and Lozano propose seven criteria that are tailored to the ethical context of contemporary neurosurgery (2010). The authors suggest that consideration for the dual role of practitioner-researcher and patient-subject implicitly grounds the criteria for clinical trials in neurosurgery. Because they fail to make it explicit, however, there remains an internal inconsistency in their recommendations to practitioners. In the face of a rapidly developing research field still in its early stages, the authors are correct in calling for cohesion in ethical standards across trials. They neglect to fully consider the need for epistemic standards, however, and for this reason their list of criteria presents a difficult set of standards for practitioners to navigate. That is, they allow that “clinical trial methodology in psychiatric neurosurgery differs significantly between centers,” and yet require that clinicians provide “data-driven, evidence-based rationale for disease & target selection that surpasses a consensus-derived threshold of information for surgical intervention” (2). Researchers cannot attain the data required for evidence-based rationale without creating the conditions for synthesis, which requires consistency of protocol among trials. The resulting gap between expectations and capability mirrors the difficulty described above when using the research ethics-based concepts of therapeutic misconception and equipoise to explain the current situation in DBS research for psychiatric indications. Lipsman et al are asking the researcher to play primarily the therapeutic role (to act with certainty toward the patient’s benefit), when the investigative role remains necessary (in order to attain such certainty in the first place). Unless the dual role of the neurosurgeon is both recognized and accommodated the appropriate ethical approach will be difficult or impossible to describe and any other approach will fail to provide guidance.

### Concluding comments.

I have shown that considering the epistemic needs of a research field in the early stages of its development can effect what ethical approach we adopt. By noting the particularities of the contemporary state of research into DBS applications for psychiatric conditions, that the patient base indeed benefits therapeutically while at the same time the need to reduce risk and increase efficacy requires that individuals in this small group be treated as subjects of research as well as patients, I have shown that the resulting dual role of the individual practitioner must be addressed. One potential consequence of directly assessing the ethical aspects of such a dual role is this: a rapidly developing field of research such as the one addressed in this paper requires open-mindedness and flexibility among practitioners to encourage consolidation of techniques and synthesis of results; my approach justifies such an attitude toward one’s own practice, even in light of the therapeutic role the procedure also plays. The primary ethical consideration becomes one of epistemic resource allocation: using available evidence to its maximal potential and emphasizing synthesis over repetition are epistemic moves that have the ethical consequence of decreasing the number of patients who must also be subjects of research.

### Notes:

1. Since the FDA granted that OCD could be treated for compassionate reasons with DBS in 2009, this has been the primary method by which such procedures have been justified. In the literature, the need for a treatment option for the 20-40% of patients with OCD or major depressive disorders who are severely impaired and yet resist pharmacological or other therapeutic options is generally given as the primary reason for continuing and increasing research into DBS for psychiatric conditions (Lakhan & Calloway, 2010; Lipsman et al, 2010; Mian, 2010; Abosch & Cosgrove, 2008).
2. Space requirements and a desire to avoid being repetitious are the reasons I will not address Phases III or IV here, which test whether safety holds for widespread use in a heterogeneous population.
3. Kimmelman (2010) argues that phase I research in the case of gene transfer studies, for example, remains at this intersection as well; here I am drawing a comparison between the general standards for Phase I trials, and will later follow Kimmelman’s lead in highlighting the differences between actual practice and this ideal.
4. There are multiple sources for this ‘idea’: the continuing use of psychosurgery led to general knowledge that lesions could be effective treatments for these patients, for example, and the history of applying electricity to the brain provides a parallel lineage. Note that these three genealogies all trace the accumulation of empirical evidence of possible correlations, far more so than they develop out of a theoretical or causal framework being applied or tested.
5. It could be argued that the advent of imaging technology and

DBS itself, being reversible and allowing for blind controls, have already enabled the field to move toward an evidence-based stance. This does not decrease the need for synthesis, however, but merely spreads it across multiple disciplines.

6. There have been questions raised as to whether the RCT format is ever suitable for the investigation of even drug treatments for psychiatric disorders, due to the complex causal structures of these disorders (Kendler 2008) and the inevitable heterogeneity of the patients for whom the treatment is designed (Hotopf 2002, Gupta 2007).
7. Again, it is hoped that the use of imaging technology will resolve this difficulty, enabling non-invasive confirmation of hypotheses about the location of related mental functions. We are far, however, from attaining the kind of data needed to do the necessary theoretical work prior to DBS implementation, so the procedure itself remains a principle investigative method, and imaging is most useful in conjunction with surgery (Abosch & Cosgrove, 2008).
8. That is, the concerns raised from the perspective of research overlap those raised from the perspective of therapy in such a way that neither the procedure itself nor the role of the practitioner allow for a simple analytic segregation of the therapeutic and non-therapeutic aspects.

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