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Ethical Issues in Deep Brain Stimulation Research for Treatment-Resistant Depression: Focus on Risk and Consent

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Abstract

Deep brain stimulation (DBS) is currently in pivotal trials as an intervention for treatment-resistant depression (TRD). Although offering hope for TRD, DBS also provokes ethical concerns—particularly about decision-making capacity of people with depression—among bioethicists, investigators, institutional review boards, and the public. Here, we examine this critical issue of informed consent for DBS research using available evidence regarding decision-making capacity and depression. Further, we explore the implications of the nature of TRD as well as that of the intervention (invasive brain surgery) for informed consent. Based on these analyses, we argue that additional safeguards specific to DBS research for TRD, beyond those that might be used in any higher risk study, are not supported by available empirical evidence. We nevertheless underscore the limited data on such invasive procedures in severely ill psychiatric patients and advocate a research agenda for the systematic study of ethical issues raised by these research endeavors.

Keywords

decision-making capacity; deep brain stimulation; depression; informed consent; neuroethics; psychiatry; research ethics

Psychiatric disorders are a leading cause of disability worldwide (WHO World Mental Health Survey Consortium 2004). These diseases are frequently chronic, treatment-resistant, and associated with significant suffering. Treatment-resistant major depression (TRD)—depression that has not responded to multiple, adequate treatment trials—exemplifies the challenge confronting mental health intervention researchers. A substantial proportion of

patients remain severely symptomatic and debilitated, some for many years, and many experience chronic suicidal ideation. While suicide is the most dramatic outcome of unremitted depression, significantly diminished quality of life itself justifies pursuing improved treatment options.

In light of this need, new treatments are actively being sought, including techniques such as deep brain stimulation (DBS) that modulate brain circuits hypothesized to be implicated in depression. DBS is an accepted intervention for individuals with severe, treatment-resistant neurological (e.g., Parkinson's disease, essential tremor, dystonia) and medical conditions (e.g., intractable pain) (Bell, Mathieu, and Racine 2009). These successes, combined with an improved understanding of the neurobiology of treatment-refractory psychiatric disorders, have led to the investigation of DBS for a number of psychiatric illnesses. Preliminary efficacy has been shown in relatively small studies of DBS for TRD, obsessive-compulsive disorder (OCD), and Tourette's syndrome (Bewernick et al. 2010; Flaherty et al. 2005; Goodman et al. 2010; Greenberg et al. 2006; Lozano et al. 2008; Mallet et al. 2008; Malone et al. 2009; Mayberg et al. 2005; Nuttin et al. 2008).

Because of its potential for alleviating suffering in people with these difficult-to-treat disorders, DBS has evoked substantial excitement. However, given the nature of these disorders and of the intervention, DBS for psychiatric conditions has also triggered ethical concerns about the potential for misuse (Fins 2003). These concerns include the possibility of widespread acceptance of the treatment before adequate safety and efficacy data are obtained, premature expansion to other conditions without appropriate justification and research, and issues related to the ability of psychiatric patients to provide fully informed consent (Bell, Mathieu, and Racine 2009; Fins 2003; Synofzik and Schlaepfer 2008).

At this stage of development of DBS for psychiatric disorders, considerations related to informed consent are of primary importance. Nearly a decade ago, Nuttin and colleagues (2003) recognized this issue and made recommendations for special safeguards for the study of DBS for OCD. However, these recommendations were not evidence-based. Over the last several years, much research has focused on informed consent for research in people with psychiatric disorders. These studies can help guide the development of ethically sound practices and policies.

Here, we examine whether severely ill individuals with treatment-resistant depression require special safeguards to ensure an ethically sound informed consent process for studies of DBS. We first examine whether patients with depression in general (i.e., not necessarily treatment-resistant) have the ability to provide informed consent. Next, we explore the implications of this specific intervention (which involves invasive brain surgery) and study population (severely ill, treatment-resistant, and often desperate patients) for informed consent. We argue that, based on the (somewhat limited) available data, an ethically sound informed consent process for DBS research in TRD patients can be insured with only modest additional safeguards—similar to those appropriate for research on other innovative, higher risk therapies. Finally, we recognize the limits of this database, particularly with respect to DBS for TRD patients, and we therefore suggest that further research is needed on informed consent and other ethical issues in research on DBS for TRD. We specifically

target TRD for two reasons: (1) It is prevalent, debilitating, and costly (Holtzheimer and Mayberg 2010); and (2) DBS for TRD is currently being tested in two large-scale, industry-sponsored clinical trials (Advanced Neuromodulation Systems Inc. 2009; MedtronicNeuro 2009). For these reasons, TRD may become the most common psychiatric indication for DBS and provides an excellent basis for ongoing neuroethics-focused research.

DECISION-MAKING CAPACITY FOR INFORMED CONSENT IN DEPRESSED PATIENTS

Although germane to all clinical research with significant risks, ethical questions carry particular weight—and tend to elicit greater concern from ethics reviewers and the general public—when research participants have psychiatric disorders. Concerns about the abilities of people with serious mental illnesses to provide informed consent for clinical research have been voiced for quite some time (Elliott 1997; Michels 2004; National Bioethics Advisory Commission 1998; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978). Institutional review boards (IRBs) may view people with mental illness as more vulnerable than people with medical disorders. The general public also perceives people with mental illnesses as having decreased decisional capacity (Muroff, Hoerauf, and Kim 2006). Such concerns, however, must be subjected to empirical investigation, rather than simply accepted at face value, to ensure the principle of justice is met (Roberts 1998).

Although psychiatric illnesses (particularly disorders of thought and cognition) do increase the risk for impaired decision-making capacity, this is not the case for all patients with mental illness (Appelbaum et al. 1999; Candilis et al. 2008; Dunn, Candilis, and Roberts 2006; Jeste, Depp, and Palmer 2006). Such worries have tended to be framed in ways that fail to differentiate levels of functioning along the vast diagnostic and symptomatic spectrum of mental illnesses, instead labeling all people with mental illnesses as likely to be impaired in their decision-making capacity for research (Roberts and Roberts 1999).

The relationship between major depression and decision-making capacity has been examined in a number of studies. For example, the MacArthur Treatment Competence Study enrolled three inpatient groups (92 people with major depression, 75 with schizophrenia, and 82 with cardiac disease), and compared each group's performance on a set of comprehensive assessment tools to that of a matched community comparison sample. On these measures (which focused on *treatment*, not research, decisions), depressed patients performed better than patients with schizophrenia, but marginally worse than cardiac patients (Grisso and Appelbaum 1995). Using a cutoff of two standard deviations below the mean of the entire sample (patients and controls combined), the vast majority of depressed patients were not impaired on the scales measuring understanding (5.4% impaired) or reasoning (7.6% impaired). Thus, a small proportion of these inpatients were deemed impaired. It should be noted that this proportion is significantly *lower* than that found more recently in studies of treatment-related decision-making capacity among medical inpatients (Raymont et al. 2004).

Other studies have focused more specifically on *research* consent capacity in depressed patients. Cohen and colleagues (2004) reported good levels of capacity among depressed

inpatients, although the patients showed more impairment than a community comparison group. Among outpatients with at least moderately severe recurrent major depression enrolling in a psychotherapy-only protocol, Appelbaum and colleagues (1999) reported very good performance on a structured capacity assessment tool (MacArthur Competence Assessment Tool for Clinical Research, or MacCAT-CR). Similarly, among ambulatory cancer patients evaluated for research consent capacity, Casarett and colleagues (2003) found no correlation between levels of depressive symptoms and the three major capacity domains measured by the MacCAT-CR; in contrast, age, education, and literacy were all associated with capacity subscales.

Guided by this available literature, insufficient evidence exists to judge depressed patients, in general, as lacking capacity for informed consent for research. There is thus inadequate justification for extraordinary safeguards (e.g., independent capacity assessments for all participants) based solely on their diagnoses. There may be other reasons for caution on the part of researchers and sponsors, however, related to the nature of the situation in which subjects find themselves and to the risk:benefit profile of the research.

RISKS AND BENEFITS OF DBS RESEARCH FOR DEPRESSION: IMPLICATIONS FOR INFORMED CONSENT

The unique aspects of DBS for severe, intractable psychiatric illness may still introduce additional concerns regarding informed consent. First, invasive brain surgery goes well beyond the typical research study involving depressed patients. To implant the DBS system, stereotactic brain surgery is used to place one or more electrodes into the brain. These electrodes are connected to subcutaneous wires, which are tunneled under the skin and connected to a subcutaneously implanted pulse generator/battery pack (IPG). This procedure itself carries risks, and there are potential additional but yet unknown risks associated with stimulating different brain regions, as might be tested for each individual research study.

Second, DBS research for TRD differs from typical antidepressant treatment trials in its complexity, duration (studies need to follow patients long-term and ensure adequate follow-up care and monitoring), and multidisciplinary nature. The long-term nature of the implant, its implications for the patient and the patient's family, and the need for ongoing monitoring require significant attention during and after the consent process. In addition, there needs to be clear delineation of the each of the research team members' roles, responsibilities, and limits thereof, which need to be communicated to the patient and family in a comprehensible way.

Do these considerations argue for a *higher* threshold for adequate decision-making capacity for DBS for TRD than is typically required for other forms of higher risk clinical research (e.g., early-stage pharmacologic trials and vaccine trials)? An argument for using a "sliding scale" for requisite capacity has been promoted in the ethics literature, primarily in the treatment context (Drane 1984), but operationalizing such a standard has been elusive. Although instruments for assessing decision-making capacity are available and have been studied in many different research contexts, from minimal-risk to high-risk protocols, and among many populations, including people with depression, these instruments do not

provide clear decision rules or cutpoints that differ depending on the risk:benefit ratio of the proposed study. [For one approach to establishing such rules, see Kim et al. (2007).] Judgments about decision-making capacity will inevitably come down to the research team's implementation of its ethical duties to respect autonomy while protecting those who may have diminished autonomy. In the case of riskier forms of research, the team must pay careful attention to these issues. Again, this is *not* more true for psychiatric research than for other forms of research, e.g., in people with advanced cancer considering an early-phase trial.

The obligation to ensure an adequate consent process also drives the next point, that investigators must make sure that participants understand the risks and benefits (and limits thereof) of DBS for TRD, and must be careful neither to overemphasize potential benefits nor to deemphasize risks.

Potential Benefits of DBS for TRD

DBS has become a well-accepted treatment for movement disorders, especially as an alternative to ablative neurosurgery for severe, medication-refractory cases. Potential advantages of DBS over ablative neurosurgical procedures include its reversibility (if side effects occur), adjustability of stimulation parameters (to optimize benefits acutely and over time), and revisability of stimulation location (if placement is not optimal). Most movement disorder patients achieve clinically significant benefit from DBS (Lyons and Pahwa 2008; Moro et al. 2010).

It is possible that DBS may offer the same potential clinical benefit for a host of psychiatric disorders. Specific to TRD, pilot data suggest a 40–60% response rate (50% reduction in symptom severity) with DBS at various targets for TRD (Bewernick et al. 2010; Lozano et al. 2008; Malone et al. 2009). Yet it must be emphasized that these data are derived from small, open-label, uncontrolled studies. Even in this severely ill, treatment-resistant population, the possibility of placebo response cannot be discounted (Goetz et al. 2008). Therefore, despite the potential for benefit, the actual short- and long-term antidepressant efficacy of DBS for TRD (at any target) is unknown.

Risks and Potential Adverse Effects of DBS

The known risks of DBS are derived almost exclusively from the movement disorders literature. Risks related to DBS surgery include intracranial hemorrhage (up to 8%, though most are not associated with significant and/or permanent neurological deficits), infection (up to 10%), and death (about 0.1%) (Deuschl et al. 2006a; Deuschl et al. 2006b; Herzog et al. 2003). Additionally, the DBS system remains implanted in the subject as long as clinically appropriate (perhaps indefinitely); currently, surgery is needed every 6 months to 5 years (depending on location and stimulation parameters) to replace the implanted battery pack. If DBS does not provide clinically meaningful benefit, or if a device component breaks, it can be removed, again requiring surgery, which is associated with additional risk. The presence of indwelling hardware comes with further potential adverse effects: Certain theft detection systems (such as metal detectors) may turn off the device; strong magnetic fields (such as those used with magnetic resonance imaging [MRI]) and certain therapies

(e.g., diathermy) can inactivate or damage the device, or cause heating of device components that could damage the brain or other tissues.

Acute and chronic intracranial stimulation itself may carry additional risks. However, these risks are largely unknown and likely depend on the specific DBS target (Appleby et al. 2007). For example, subthalamic nucleus DBS may be associated with an elevated risk of suicide in Parkinson's patients (Voon et al. 2008), and anterior internal capsule DBS may be associated with mania in TRD and OCD patients (Greenberg et al. 2008; Malone et al. 2009). Again, given the small number of patients studied to date for all psychiatric indications, it is expected that additional adverse effects of acute and chronic stimulation at various targets will be identified over time. Thus, there is a degree of *unknown* risk, which must be considered when deciding whether or not to participate in a clinical trial of DBS for a novel indication.

In summary, it is clear that DBS is associated with benefits of unclear dimensions as well as significant risks and potential harm; arguably, the risks associated with DBS are greater than any other available treatment in psychiatry. Understanding these risks, evaluating them in the context of one's own circumstances, and weighing them against the alternatives is the patient's task when considering whether to participate in any research study. Does DBS research for TRD raise any unique issues, then, with regard to how informed consent should be conceptualized or how the process itself ought to proceed? The answer to this question relates directly to the nature of TRD itself—its treatment resistance, specifically, and the possibility of desperation on the part of patients.

THE NATURE OF TRD: IMPLICATIONS FOR INFORMED CONSENT FOR DBS RESEARCH

The risks associated with DBS for TRD must be considered in the context of an underlying condition that is demoralizing, severely disabling, and for which no amelioration is expected with available treatments. Some subset of these patients may be desperate for relief; others may be leery of “new and improved” treatments after having been repeatedly disappointed. Are some patients so desperate that their decision making is affected to the point where we should not accept their informed consent (all other things being equal)?

We note that the possible effects of desperation on decision making are by no means unique to psychiatric research (Roberts 1998). Thus, severe TRD is potentially no different from cancer, end-stage heart or lung disease, or multiple sclerosis (to name a few). As with these other serious, potentially life-threatening illnesses, a reasonable person—with full decision-making capacity—may decide to assume such risks for even a small chance of benefit—sometimes (but not always) with concurrent altruistic motivation to advance knowledge about potential interventions (Daugherty et al. 1995). In our current research study, we are finding that participants considering enrolling in DBS studies for TRD demonstrate a combination of hope for personal benefit and recognition of the constraints as to what is known about the benefits, and many articulate the desire to help others with this debilitating condition. But participants who express an overly optimistic perception of their potential for direct benefit from DBS for their depression cannot be presumed to lack capacity (any more

so than advanced cancer patients who hope that they will benefit from a phase I trial). It is critical, however, that investigators clarify that uncertainty about the benefits of the intervention (equipoise) is precisely why the research needs to be done.

A critical issue then becomes: How does a desperate and severely ill person weigh risks and benefits when considering participation in such early-stage research? Unfortunately, there are few available data to help answer this question in general or as it applies to DBS for TRD or any other neuropsychiatric condition. Although some bioethicists worry that people with depression will discount risks to themselves *because* of their depression (and hence, presumed lack of self-concern) (Elliott 1997), this has not been empirically validated. In the study by Cohen and colleagues (2004) described earlier, patients distinguished between risk levels of two separate protocols (a phase III pharmacologic trial, and a study of ketamine administration plus a neuroimaging procedure). The depressed patients were less willing than comparison subjects to volunteer for both types of trials, suggesting that depression itself did not cause patients to discount the risks of biomedical studies. Two additional studies of hospitalized, depressed patients providing consent for electroconvulsive therapy (ECT) found no relationship between (treatment-related) decision-making capacity and depression severity (Lapid et al. 2004; Lapid et al. 2003). Thus, from the small database available, depression severity in and of itself does not seem to lead to patients disregarding personal risks.

However, desperation may arise not from symptom severity so much as from intractability and the lack of available treatments. For some individuals, the prospect of indefinite suffering (i.e., no end in sight) may tip the balance in favor of enrolling in higher risk research, with its attendant uncertainties, for even a relatively poorly quantified potential benefit. A primary concern is that desperate patients may, in some sense, not *truly* possess autonomy: By this reasoning, patients with no other reasonable treatment options effectively have no real choice regarding participation. Related to this, one might worry that desperate patients may minimize potential harms of participation and/or overestimate the chance of personal benefit—which, when they occur, could be considered distortions in judgment. To reiterate, this issue is not unique to psychiatry.

A simple solution to this potential problem would be not to include desperate patients in clinical trials at all, especially not randomized controlled trials. This is not acceptable, however, since for some conditions (e.g., metastatic cancer, amyotrophic lateral sclerosis, chronic pain, or severe TRD), many patients will be desperate. Provided that other aspects of decision-making capacity are intact, respecting autonomous decision making by people with serious illnesses demands equal respect for decisions entailing higher risk as for those involving less risk. Thus, not allowing desperate patients into research prevents any scientifically valid investigation of potentially beneficial interventions—and violates the principle of justice. Still, it is noted that, to date, these conclusions are based primarily on theoretical arguments. Few available data guide us on how desperation affects decision making (Appelbaum, Lidz, and Klitzman 2009); therefore, this should become a focus of ongoing ethical investigation.

Another solution would be to place desperate patients only in an active treatment arm and only randomize those patients who are truly indifferent to which treatment they receive and who are seeking enrollment only to advance science (Minogue et al. 1995). This solution is also problematic, as Logue and Wear (1995) have effectively argued. If there is any chance of benefit from a proposed intervention, it is difficult to see how a truly desperate patient could really be indifferent: In the case of severe, intractable pain, the chance that a new intervention might improve one's condition will almost always make it the treatment of choice. One proposed requirement for allowing presumably desperate patients (although even defining what this means may be problematic) to participate in clinical trials is that there must be true scientific, expert equipoise regarding the safety and efficacy of the treatment (Allmark and Mason 2006). This requirement, however, ought to be identical to that for investigations involving people with other serious or life-threatening illnesses.

A practical way to deal with concerns about desperation is of course to ensure a thorough consent process. This process must delve more deeply than what is outlined in the typical consent forms, which are not individualized to specific patients' concerns and questions, are overly detailed and technical (despite requirements for readable consent forms), and are frequently seen as legalistic. The investigator must take as much time as is needed (up to several hours, in our experience), to seek the participant's, and any family members', questions, concerns, motivations, and potential misperceptions (whether in terms of risks or benefits). It is only with an in-depth interaction with a knowledgeable investigator that the potential participant can explore all aspects of these complex proposed protocols. In light of the recent Humanitarian Device Exemption for DBS for OCD, a similarly thorough consent process, with ample opportunity to clarify or correct any misperceptions or misplaced expectations (whether about risks or benefits), should be enacted for these potential treatment candidates as well (Glannon 2010).

INFORMED CONSENT FOR STUDIES OF DBS FOR TRD: PRELIMINARY RECOMMENDATIONS

Based on the foregoing, we reach the following conclusions:

1. Depressed patients in general do not *prima facie* have significantly impaired decision-making capacity. However, as with all potential research subjects, possible factors that might affect capacity should be thoughtfully considered in the informed consent process.
2. Highly invasive and potentially risky interventions do not necessarily require special safeguards to insure an adequate informed consent process, beyond what should apply in any clinical trial. However, the nature of a particular trial (in terms of specific risks, uncertain benefit, complexity, etc.) may require additional steps to insure that subjects have understood the information necessary to make an autonomous decision. It would be prudent to build in such measures in early-stage DBS trials.
3. Severity and intractability of disease may reasonably alter an individual's valuation of risks and potential benefits when considering an intervention. There is no reason

to assume, however, that severe intractable depression is unique compared to other equally distressing, disabling, treatment-refractory conditions. The inclusion of desperate patients in clinical trials is ethical and in appropriate circumstances may actually be required for the principle of justice to be met.

4. The preceding conclusions are based in part on a limited but growing database, but rest more on theoretical arguments. A significant gap exists in the ethics literature concerning the decision-making capacity of TRD patients and the effects of desperation on the consent process.

A RESEARCH AGENDA FOR EMPIRICAL STUDY OF THE ETHICS OF DBS IN PSYCHIATRY

Many of the issues raised in the preceding discussion can and should be a focus of ongoing ethics research. With the roll-out of large, multicenter trials to study the effects of DBS in TRD subjects (and potentially other psychiatric populations), an excellent opportunity is presented to do this. We propose two main areas for investigation.

First, decision-making capacity among severely ill, TRD patients should be more carefully investigated. Numerous instruments exist for this purpose (Dunn et al. 2006) and can be adapted to each specific protocol. We are currently conducting an investigation using the MacCAT-CR in TRD patients who are considering enrollment in independent studies of DBS at Emory and Columbia universities. We strongly recommend that all investigators focused on TRD consider the inclusion of additional measures to assess decision-making capacity to answer the questions that exist regarding these research subjects. We further encourage investigators to examine the effects of enhanced consent procedures on the adequacy of the consent process (Flory and Emanuel 2004; Palmer et al. 2008). Such research will be easier if IRBs allow more leeway for modified consent procedures for conducting research on these procedures themselves—without additional burdensome “meta-consent” procedures (given that investigations of informed consent are themselves minimal-risk studies) (Saks, Dunn, and Palmer 2006).

Second, the effects of desperation on decision making should be explored. This research should not be limited to studies of TRD and DBS but could include many other fields (oncology, neonatology, neurology, end-stage diseases such as renal failure, chronic obstructive pulmonary disease, etc.) and patient populations. Instruments will need to be developed that assess a patient’s attitudes toward likelihood of benefit and harm, sense of altruism, and views toward research in general. In Table 1, we provide sample questions from one such instrument (full scale available from the first author). Along these lines, it would be worth pursuing the potential influence of the perspectives and desperation of others (family members, friends, other treatment providers) on the decision making of the patient.

Third, as neuroethics as a field matures, and as DBS research involving people with psychiatric conditions evolves, it will be critical to assess long-term direct and indirect effects of these neuromodulation devices—the goal of which is to alleviate the suffering of

patients—on other aspects of patients' lives, and on how patients and their loved ones feel about and respond to these changes.

CONCLUSION

DBS research in psychiatry holds promise, but clearly raises ethical challenges, especially in the area of informed consent. We have argued that depressed patients, in general, should not be presumed to have diminished decision-making capacity simply due to having a mental illness, and that most depressed patients likely retain adequate decision-making capacity. We further conclude that DBS research in TRD is not unique in the concerns raised related to informed consent and that it should be treated as are other higher risk research studies—i.e., with extra attention to insuring that subjects have understood the information about the study. We finally recognize that desperation in cases of extreme, end-stage illness may affect individuals' weighing of risks and benefits when considering participation in research—however, there is currently no acceptable justification for excluding desperate subjects from clinical trials, even of potentially harmful interventions. Finally, we note that many of these conclusions are based on extrapolation and theoretical arguments, and the actual evidence base is severely limited. A broad research agenda is needed for studies going forward.

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Table 1

Instrument to assess motivations and perceptions of risks and benefits in study of DBS for TRD: Sample questions

1. What would you say is the <i>main purpose</i> of this research project? That is, why are the researchers doing it?				
2. How <i>likely</i> do you think it is that you <i>personally</i> will benefit from being in this study?				
Very unlikely				Very likely
1	2	3	4	5
Please explain your rating:				
What types of benefits do you think you might get? In other words, are there specific symptoms that you have that you think will get better?				
Why do you expect those benefits?				
3. To what degree is the desire to help others in the future a motivation for your participating in this study?				
Very little				Very much
1	2	3	4	5
Please explain your rating:				
4. How risky do you believe this study is to you, <i>personally</i> ?				
Very safe				Very risky
1	2	3	4	5
Please explain your rating:				
5. Please rate your agreement with this statement: In my opinion, the possible benefits to me outweigh the personal risks of being in this study.				
Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1	2	3	4	5
6. Did you discuss with your family whether you should enroll in the DBS study?				
Yes	No			
If NO: Did you want to (or try to) discuss with your family, whether you should enroll in the study?				
If YES: What do you think was important or helpful in that discussion?				
7. In what ways might having the stimulator affect how you think about your depression?				