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Beyond Mere Symptom Relief in Deep Brain Stimulation: An Ethical Obligation for Multi-faceted Assessment of Outcome

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Abstract

Assessment of outcome following Deep Brain Stimulation (DBS) has traditionally focused on symptom specific and quality of life measures. Greater attention needs to be paid to the diversity of patient goals and values, as well as recognition of the shifting nature of those goals over the course of DBS therapy. We report preliminary data from an empirical study examining patients' goals with respect to DBS in the treatment of Parkinson disease. We argue that a multifaceted assessment of outcome over time, including well validated symptom measures, quality of life, functional and patient specific metrics, is ethically necessary in order to fulfill fiduciary and professional responsibilities. These assessments should be augmented with a deliberative multi-disciplinary process of review and evaluation. Such an approach will lead to improved informed consent, promote better clinical research, and facilitate good patient care by providing a systematic mechanism for capturing and acting on important patient insights. These processes become increasingly critical as DBS begins to be applied to neuropsychiatric disorders.

Keywords

Deep Brain Stimulation; professional ethics; informed consent

Traditional symptom specific and quality of life measures may be insufficient in evaluating successful outcomes following deep brain stimulation (DBS). This is problematic in the context of established DBS indications and even more so as DBS for neuropsychiatric disorders moves into the therapeutic domain. DBS is an elective neurosurgical procedure intended to improve a patient's quality of life. Consequently, greater attention needs to be paid to the diversity of patient goals and values, as well as recognition of the shifting nature of those valued goals over the course of DBS therapy. These two themes have emerged prominently in a study we are conducting that examines patient goals for DBS. In reflecting on our preliminary data, the importance of the evolving nature of individual patients' goals for DBS in the informed consent process, both for current FDA approved indications and upcoming uses in neuropsychiatric disorders, becomes apparent. We advocate for extending the widely accepted model of multi-disciplinary teams in the selection and care of DBS patients to include the adoption of multi-faceted outcome assessments that incorporate formal assessment of patients' goals. Even though this practice may result in increased

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resource utilization, such a model allows for more robust considerations of the diversities of legitimate goals for DBS and leads to a deliberative process that is respectful of professional obligations as well as fiduciary responsibilities to patients.

PARKINSON DISEASE AS AN EXAMPLE: AN EMPIRICAL ETHICS STUDY

Outcome following DBS for Parkinson Disease (PD) has been traditionally assessed using the motor scale of the Unified Parkinson Disease Rating Scale (UPDRS-III; Fahn & Elton 1987). This measure examines tremor, rigidity, speech, facial expression, fine motor skills, posture, gait and bradykinesia. Quality of life in Parkinson disease is commonly assessed using the Parkinson Disease Quality of Life Measure (PDQ-39; Peto et al 1998, Jenkinson et al 1997). The PDQ-39 consists of questions that cover the following eight domains: Mobility; Activities of Daily Living; Emotional Well-Being; Stigma; Social Support; Cognition; Communication; and Bodily Discomfort. Multiple studies have documented beneficial outcome following DBS for PD with respect to standard symptom measures and quality of life (e.g., Deuschl et al 2006; Follett et al 2010). Nonetheless, researchers have highlighted the limitations of the UPDRS-III with respect to assessing outcome. For example, Kleiner-Fisman and colleagues (2010) argue that motor impairment, in and of itself, does not reduce health related quality of life in PD. Reductions in health related quality of life more often reflect the consequences of poor motor function, such as difficulties with activities of daily living or loss of independence. Although the disconnect between standard symptom outcome measures and quality of life has been documented in Parkinson disease, no studies have explicitly examined the extent to which DBS therapy addresses individually defined symptom and behavioral goals from a patient perspective.

As part of a larger study, we enrolled a series of 15 patients with PD who underwent DBS surgery as standard of care. They were consented to participate in an IRB approved study examining beliefs about symptom control and personal control following DBS. We operationally defined personal control as the ability to participate in individually defined activities or behaviors that influenced subjects' decisions to seek out DBS. Subjects completed visual analog rating scales prior to surgery and at a second time point that was approximately three months following implantation of the DBS electrode, usually at the time of the second programming session after approximately one month of stimulation (mean days on stimulation = 36). Our data provide a unique and systematic window into patients' stated goals for surgery, and hence, insight into their judgments about successful outcomes.

The majority of subjects were men ($n=12$) with an average age of 59.27 ($sd=8.53$) at surgery and a mean of 9.53 years ($sd=4.69$) years of Parkinson disease. No subject had undergone a previous neurosurgical procedure for treatment of PD symptoms. Consistent with other published series, our subjects had severe symptoms with the average off medication UPDRS-III score of 43.21 ($sd=11.14$) and an on medication UPDRS-III score of 21.93 ($sd=9.43$). Subjects endorsed relatively high scores on the PDQ-39 Summary Index, indicative of reduced quality of life, with a mean of 32.31 ($sd=16.60$).

Of specific interest for our study were the subjects' reports of symptom and behavioral goals. Subjects were asked to provide the top three to six symptoms they expected to be reduced following DBS therapy. These symptoms were rank ordered and the subjects were instructed to rate the present symptom severity and expected future severity following DBS therapy on a visual analog rating scale with 10 representing the greatest severity. Similarly, subjects were asked to provide the top three to six behavioral goals or activities that they expected to improve following DBS therapy. These were rank ordered and the subjects rated the limits to their ability to participate in these activities at the present time and their

expectations following DBS therapy with 10 representing the most severe limits to their participation.

Our subjects reported expectations of relief in a number of symptoms including reductions in the core motor symptoms of PD, e.g., tremor, rigidity, bradykinesia (slowed movement) and balance. In addition, subjects sought out DBS to improve pain, fatigue, dyskinesias (excess movements), speech, medication side effects and memory. (Please see Table 1 for a list of subjects' reported top three symptoms). As highlighted in the Table, it is important to note that more than one third of the reported symptoms of greatest concern are not assessed with the UPDRS-III. Most subjects expected DBS therapy to result in dramatic improvements in their symptoms with the average expected future symptom severity rating for the top three symptoms of 1.65. When one compares the expected symptom severity at baseline to the actual symptom severity rating at the post-operative assessment, discrepancies were evident such that most subjects expected greater improvements than they received at the early post-stimulation point. Despite these discrepancies, subjects indicated statistically significant improvements in their individual symptoms following DBS (t statistics ranged from 4.85 – 5.52 all values of $p < 0.05$). Subjects were also provided their original list of symptoms in alphabetical order at the post-operative assessment and asked to rank the symptoms with respect to which is the most important symptom they expect to see improved. All subjects changed their rank ordered symptom lists relative to the ranking they provided at baseline and the majority of subjects added additional symptoms. In summary, subjects appeared to overestimate the benefit they would receive, but still appreciated a significant improvement. Further, the order of importance associated with specific symptoms changed on retrospective review.

In a similar vein, the data indicate that subjects' goals for seeking out DBS with respect to their ability to participate in valued activities varied considerably. All subjects reported a minimum of three goals or activities. The activities could be loosely grouped into seven broad domains: Leisure (e.g., wood working); Family Social (e.g., playing with grandchildren); Other Social (Church activities); Work (e.g., household chores or paid employment); Activities of Daily Living (e.g. drinking from a cup); Exercise; and Driving. (Please see Table 2 for a list of subjects' reported top three behavioral activities). Once again, most subjects expected dramatic improvements in their ability to participate in these activities when asked at baseline to predict their severity ratings following DBS therapy (mean expected severity rating = 1.35). Not surprisingly, when one compares subjects' expected future activity ratings at baseline to their actual severity ratings following surgery, most subjects expected greater improvements than they received at the early post-operative period. Nonetheless, statistically significant improvements in the subjects' ability to participate in these individually defined valued activities were evident following DBS therapy after only approximately one month of stimulation (t statistics ranged from 4.57 – 6.67, all values of $p < 0.05$). The vast majority of subjects (14/15) changed their rank ordered list of valued activities at the three month assessment and approximately half ($n=7$) added new activities. The PDQ-39 has several items that assess some of our broadly defined categories, such as "difficulty doing the leisure activities you would like to do" or "difficulty looking after your home," and some more specific items such as "difficulty holding a drink without spilling it." Many of the items on the PDQ are symptoms or medication side-effects associated with PD (e.g., cognitive changes, speech changes, fatigue and pain). But there are no specific items in the PDQ-39 that address positive social goals, work, driving or many of the other specific goals in the manner that our patients expressed.

These preliminary data are informative for a number of reasons. First and foremost, our findings indicate that the most widely used disease specific symptom and quality of life measures may not assess those symptoms and behavioral goals that are most important to

patients with PD who seek out DBS. Second, prior to surgery, patients expect that DBS therapy will result in significant improvements in virtually all individually identified top symptom and behavioral goals. This is not an unexpected result given the findings by Bell and colleagues regarding the prevalence of “hope” described by DBS providers (Bell et al 2010). Most patients expected greater improvements in their symptoms and desired activities than they reported receiving following one month of stimulation. Finally, patients’ goals and expectations for DBS evolve over time such that improvements in specific symptoms and desired activities may become more paramount over time while other symptoms and goals lessen in importance. This implies that, at least during the initial few months following DBS surgery, patients’ expectations regarding DBS continue to evolve in a dynamic manner. This is in contrast to the standard medical approach to defining success that is static and limited to assessment of symptoms at a specified time point.

APPLICATION TO NEUROPSYCHIATRIC DISORDERS

Consideration of the informed patient’s definition of successful surgery is particularly important in functional neurosurgery teams in which the intervention is an elective procedure designed to improve the patient’s quality of life. Hence by its very nature, the patient’s primary goals for functional neurosurgery may be much more subjective, complex, and value laden than simple symptom relief. In order for these preferences to be meaningfully integrated into a patient care setting, a framework needs to be established that includes explicit assessment of patient goals over time. A multi-disciplinary team model may provide such a structure. A multidisciplinary team approach to patient care has been implemented in many functional neurosurgical programs, including Deep Brain Stimulation (DBS) centers. Each healthcare specialist views the patient through their own “lens” with specific attention to symptoms, behaviors, and goals that are particularly important to their specific discipline (Ford & Kubu, 2006). These inherent biases and perspectives influence the evaluations of outcome success following surgery. These biases can impact, in an iterative fashion, both the surgical candidacy decision making and informed consent processes in future cases.

We argue for the need for clear systematic discourse involving the DBS team and patient so that an even more explicit and ethically robust decision making process regarding the determinations of successful outcome following DBS will emerge. Although few healthcare teams would disagree with this approach, clinical schedules and other time demands present significant challenges to thoughtful attention and discussion of potential differences between the various specialists’ and patient’s values and goals that influence treatment decisions and assessment of outcome. We contend that good ethical practice is enhanced by making these potential differences transparent and engaging in open dialogue. This conversation will then influence decisions regarding surgical candidacy and informed consent. This is especially important in light of the expansion of DBS to new indications, particularly neuropsychiatric disorders such as depression, addiction, and dementia.

The lessons gleaned from our experience with patients with PD can inform our understandings of the outcomes evaluations following DBS for neuropsychiatric disorders. Several authors have already commented on the need for multidisciplinary assessment of candidates for DBS for the treatment of neuropsychiatric disorders (Nuttin et al, 2002; Fins et al 2006). We concur that this is of critical importance. Perhaps due to the increased ambiguity associated with measuring some neuropsychiatric symptoms coupled with the legacy of abuse of psychiatric surgeries in the past, there is a stronger obligation to put in place a deliberative process that involves a broad spectrum of professional perspectives that can better account for stakeholders’ interests in assessing outcomes in DBS for neuropsychiatric disorders.

First, similar to the PD literature, we need to have objective, reliable, and valid measures of symptom severity and quality of life. This is critical in order to communicate results to the broader research community and foster appropriate clinical research as we explore the safety and potential benefits of DBS in these new indications. These measures should not be thought of as sufficient for discharging our fiduciary duties to evaluate outcomes for any particular individual in a clinical setting. Symptom specific measures may operate only as crude proxies for what can be discovered in the inherently richer and more value-laden patient narratives that take more time and empathy to elicit. We should not discount the knowledge gained through interacting with patients as they meet with different disciplines. Best practice in a multi-disciplinary team provides opportunities for various providers to give voice to these types of knowledge.

Second, we need to consider outcome assessment from a safety perspective. Safety measures should include surgical, medical and neuropsychological metrics. Operational definitions for adverse events and serious adverse events have been offered by the FDA. Identification of the appropriate safety measures should be guided by knowledge of the underlying disorder and the functional neuroanatomy of the circuit targeted. Harms measured by neuropsychological testing should be given similar weight as those accorded to medical and surgical outcomes. Given the early nature of this work, it will be critically important to carefully and systematically document any meaningful change, either for the positive or negative. It is important to recognize that adverse events or unexpected effects in a clinical setting may lead to further scientific discovery and potential new interventions (Fins et al 2011). These data should be aggregated in order to promote quality improvement as well as to inform future innovations and research

Finally, we need to consider the patient's goals for seeking out DBS and their ratings of benefit in achieving those goals. This explicit reporting can help the multi-disciplinary team evaluate the appropriateness of moving forward with DBS in an individual patient. It may also enrich the informed consent process by creating a better appreciation of the potential limits of benefit for some of the patient's primary goals. This entails a systematic process in which the patient's expectations for symptom relief and, perhaps even more importantly, the behavioral goals that have compelled them to seek out surgery are specifically elicited. A process of continued systematic collection of these data will allow for future quality improvement assessment. This can lead to better predictive models of patient defined success that can be used as a tool in helping specific patients decide whether to pursue DBS.

Our data with PD patients indicate patients' goals for both symptom relief and behavioral activities are not fully assessed using the most widely used outcome metrics. This may also hold true for patients with neuropsychiatric disorders. We suspect that, similar to our PD patients, some neuropsychiatric patients will express goals that include returning to work or school, improved social relationships, or resumption of valued hobbies. Consequently, specific functional measures such as job or education status may be more important metrics to patients for tracking successful treatment than symptom reduction on a standardized rating scale.

In addition, our data suggest that patients' symptom and behavioral goals evolve over time such that goals that were paramount prior to surgery may lessen in importance and other goals may become more important. The dynamic and evolving nature of patients' goals for DBS therapy, which may extend well beyond the traditional six month post-operative outcome assessment point, is a critical consideration. These data suggest that systematic assessment of patient's symptom and behavioral goals for DBS needs to occur regularly over the course of the therapy and that we should not assume that those goals articulated prior to surgery continue to be primarily important to the patient after surgery. This

reassessment of goals at various time points will provide an opportunity for the multi-disciplinary team to better understand the patient's experience of the disorder while receiving DBS and better assess outcome which may then lead to stimulation changes, additional treatments or education as needed. The extent to which these potential changes in goals and values may reflect contextual effects, disorder specific changes (i.e., symptom amelioration or disease progression), or actual changes in patients' values remains to be addressed and are important research questions in their own rights.

One of the unique challenges in assessing neuropsychiatric patients' evaluations of success, with respect to both symptom and behavioral goals, is that the underlying neuropsychiatric disorder and treatments may hinder patients' ability to make objective appraisals of their own behavior (e.g., Synofzik & Schlaepfer 2011; Thames et al 2011). Reduced insight is a cardinal symptom of many neuropsychiatric disorders, particularly cognitive disorders such as dementia, such that patients may report that their memory is better than objective measures document. Mood disorders may result in self-reported over-estimates of cognitive dysfunction or other core symptoms. This raises a potential ethical tension between which, or whose, definition of successful outcome should take priority given the disorder under treatment may hinder a patient's ability to fully appreciate benefit or adverse side-effects.

CONCLUSION: NEED FOR FURTHER WORK

Research is necessary in how to best shape the consent and outcomes assessments in the application of DBS to neuropsychiatric disorders. We recognize the potential challenges in obtaining "valid" self-report data from patients with neuropsychiatric disorders. We argue that despite these potential challenges, clear understanding of the patients' perspective, specifically their "lived life," is critically important given the elective nature of the surgery and the primary goal of improving quality of life. Systematic assessment of patients' specific symptom and behavioral goals prior to surgery will reveal if patients' goals are potentially unrealistic and provide the team with the opportunity to intervene via educational efforts. Further, we hypothesize that the patients' individual cognitive and psychological strengths and weaknesses will influence their self-report of successful outcome. We can begin to better understand the complex factors that go into patient's determinations of treatment success by asking patients what their goals are for DBS, systematically evaluating the extent to which DBS helps them achieve their individual goals, and examining the extent to which cognitive, personality, and disease specific variables may impact those ratings of treatment success. This knowledge is critical to improving the informed consent process and ensuring that new innovative therapies truly meet the goals of those they were designed to help.

In conclusion, we assert that patients' goals for DBS are important and need to be systematically assessed. Determinations of success following DBS for neuropsychiatric disorders should incorporate rich subjective patient input as well as reliable and validated measures. This is both for the benefit of the patient as well as to further care through innovation and research. We argue for a multi-faceted assessment of outcome that mirrors the stated value of a multi-disciplinary team and includes standard disease specific, safety, functional, and patient specific metrics. Further, determinations regarding outcome following DBS should occur in the context of the richly diverse and deliberative process that the best practice multi-disciplinary teams provide. Our hope is that *all* of these data will provide us with a better appreciation of the underlying disease process and patients' experiences. This information will lead to better understanding, better science, and ultimately better patient care; thereby allowing the medical specialists who care for these patients better fulfill their ethical obligations to the patient, the profession, and the scientific community.

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Table 1

Subjects' Top Reported Symptoms (% Subjects) (Symptoms not assessed by the UPDRS-III in bold)

<u>Symptom 1</u>	<u>Symptom 2</u>	<u>Symptom 3</u>
Tremor 33.3%	Gait-Freezing 20%	Rigidity 20%
Gait-Balance 26.7%	Dyskinesias 20%	Dyskinesias 20%
Gait Freezing 6.7%	Tremor 13.3 %	Med Side Effects 13.3%
Med Side Effects 6.7%	Fatigue 13.3%	Tremor 6.7%
Pain 6.7%	Fine coordination 13.3%	Gait-Freezing 6.7%
Bradykinesia 6.7%	Pain 6.7%	Memory 6.7%
Fatigue 6.7%	Speech 6.7%	Gait-Balance 6.7%
Off State 6.7%	Gait-Balance 6.7%	Fatigue 6.7%
		Fine coordination 6.7%
		Other 6.7%

Table 2

Subjects' Top Reported Activities (% Subjects)

<u>Activity 1</u>	<u>Activity 2</u>	<u>Activity 3</u>
Driving 20%	ADL-eating 20%	Work 30.7 %
Social-Family 20%	Driving 13.3%	Exercise 20%
Hobbies 20%	Chores 13.3%	ADL-drinking 20%
Social-Other 6.7%	Exercise 13.3%	Social-Other 13.3%
Riding scooter 6.7%	Medication Costs 13.3%	Social-Family 6.7%
ADL-Dressing 6.7%	Social-Family 6.7%	Driving 6.7%
Exercise 6.7%	Social-Other 6.7%	Chores 6.7%
	Speech 6.7%	
	Hobbies 6.7%	

ADL=Activities of Daily Living