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Ethical Considerations in Deep Brain Stimulation for the Treatment of Addiction and Overeating Associated With Obesity

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Abstract

The success of deep brain stimulation (DBS) for movement disorders and the improved understanding of the neurobiologic and neuroanatomic bases of psychiatric diseases have led to proposals to expand current DBS applications. Recent preclinical and clinical work with Alzheimer's disease and obsessive-compulsive disorder, for example, supports the safety of stimulating regions in the hypothalamus and nucleus accumbens in humans. These regions are known to be involved in addiction and overeating associated with obesity. However, the use of DBS targeting these areas as a treatment modality raises common ethical considerations, which include informed consent, coercion, enhancement, threat to personhood, and manipulation of the reward center. Pilot studies for both of these conditions are currently investigational. If these studies show promise, then there is a need to address the ethical concerns related to the initiation of clinical trials including the reliability of preclinical evidence, patient selection, study design, compensation for participation and injury, cost-effectiveness, and the need for long-term follow-

up. Multidisciplinary teams are necessary for the ethical execution of such studies. In addition to establishing safety and efficacy, the consideration of these ethical issues is vital to the adoption of DBS as a treatment for these conditions. We offer suggestions about the pursuit of future clinical trials of DBS for the treatment of addiction and overeating associated with obesity and provide a framework for addressing ethical concerns related to treatment.

Keywords

deep brain stimulation; addiction; substance dependence; overeating; obesity; ethics

Neurosurgeons, neuroscientists, and collaborating medical fields are investigating new indications for deep brain stimulation (DBS), given the demonstrated safety and efficacy of DBS for the treatment of movement disorders (Deuschl, et al. 2006). Evidence from functional neuroimaging research supporting a neuroanatomic basis of various neurologic and psychiatric disorders has prompted researchers to consider DBS for patients with severe and treatment-refractory psychiatric diseases. Subsequently, studies of DBS for obsessive-compulsive disorder (Greenberg et al. 2006; Nuttin et al. 1999), Tourette syndrome (Servello et al. 2008; Visser-Vandewalle et al. 2006; Ackermans et al. 2011), major depressive disorder (Kennedy et al. 2011; Mayberg et al. 2005), and cluster headache (Fontaine et al. 2010) have been conducted with encouraging results. Studies implicating dysfunction of the hypothalamus and reward systems in the pathogenesis of diseases, such as addiction and eating disorders associated with obesity (Berthoud et al. 2011; Stoeckel et al. 2008), have inspired proposals and further investigation into the potential therapeutic role of DBS for these disorders (Halpern et al. 2008; Torres et al. 2011; Stelten et al. 2008). In addition, these studies have supported the safety of targeting the hypothalamus and nucleus accumbens (NAc) in humans.

Currently, the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* lists substance dependence and substance abuse as different diagnoses, regardless of the legal status of the used substance. Substance dependence, or addiction, is defined as a chronic relapsing disease characterized by both physical and psychological dependence and withdrawal symptoms following the discontinuation of drug use (Le Moal and Koob 2007). The diagnostic criterion for substance abuse is mainly defined as the recurrent use of the substance despite social or legal consequences. It is associated with various medical complications including infection (Napoli et al. 2010), stroke (Toossi et al. 2010), lung and liver disease (“2004 United States Surgeon General’s Report: The Health Consequences of Smoking” 2004), and increased mortality (Fridell and Hesse 2006). Indeed, studies reveal an increased mortality rate among young opiate addicts compared to nonaddicts, with an annual estimated mortality rate of approximately 2% (Haastrup and Jepsen 1988; Oppenheimer et al. 1994). When taking into account health care costs and productivity losses, the economic cost associated with addiction to illegal substances in the United States is estimated to be approximately \$180 billion annually (ONDCP 2004).

Obesity is defined as a condition of abnormal or excessive fat accumulation in adipose tissue, such that health may be impaired, and it is characterized by a body mass index (BMI)

of greater than 30 kg/m² ("Obesity: Preventing and Managing the Global Epidemic, Report of a WHO Consultation" 2000). Obesity is not listed in the *DSM-IV*, and is not currently planned to be included in the next edition. However, the addition of binge eating has been proposed as a new diagnosis under the category of eating disorders on the basis of more recent neurobiological research showing similarities in the underlying brain mechanisms of compulsive binge eating and compulsive consumption of drugs (Volkow and O'Brien 2007). In addition to eating disorders, sedentary lifestyle, social conditions, emotional eating, availability of highly caloric food, and alteration in neural networks related to impulsivity and sensibility to reward can all induce excessive calorie intake and weight gain. Like addiction, obesity is associated with a high risk of disability and premature death (Fridell and Hesse 2006; Visscher and Seidell 2001). Obese individuals are at risk for cardiovascular disease, type 2 diabetes, and mood-related disorders, such as major depressive disorder (Bean et al. 2008; Luppino et al. 2010), and more than 30,000 annual deaths are attributed to obesity nationwide (Allison et al. 1999). Health care expenses related to obesity in the United States between 1998 and 2000 were estimated to be \$213 billion (Flegal et al. 2010). Despite aggressive behavioral, pharmacological, and surgical interventions, many patients do not succeed in losing weight permanently. Compared to the best available treatments, decision analysis studies justify research into DBS as a future alternative for the treatment of patients with addiction (Stephen et al. 2011) and treatment-refractory eating disorders associated with obesity (Pisapia et al. 2010).

DBS for addiction and obesity shares many of the ethical quandaries associated with DBS for movement disorders (Bell et al. 2009); however, fundamental differences between the movement disorder and psychiatric patient populations give rise to unique ethical issues. Moreover, some believe that addiction and obesity related to eating disorders are behaviors that share common neural targets for DBS, namely, the NAc, and thus share specific target-related ethical considerations. As investigators continue to pursue testing DBS for these conditions, it is imperative that neurosurgeons and allied health professionals have an understanding of the ethical considerations of expanding the application of DBS to these pathologies. In this article, we describe the preclinical and clinical evidence supporting DBS for disorders of behavior and call attention to several ethical issues related to the investigation and use of DBS for the treatment of addiction and overeating associated with obesity.

BIOLOGICAL BASIS OF DISEASE

Addiction and obesity induced by disordered eating are both disorders of behavior and thought that result, at least in part, from dysfunction of reward circuitry and the inhibitory control system within the cortico-basal ganglia-thalamocortical loops (Stelten et al. 2008). The proposed mechanism of DBS is modulation of an electrical imbalance at the level of this pathway to reduce symptoms. The NAc is a common target of interest due to the central role played in the reward system in both disease states; this region is cited by several authors as being especially promising, among current DBS targets, for the treatment of obesity and addiction (Halpern et al. 2011; Luigjes et al. 2012). The reward system consists of dopaminergic neurons that project from the ventral tegmental area to the striatum, including the ventral striatum where the NAc is located, and to the amygdala, septal nuclei, prefrontal

cortex, and cingulate cortex (Lubman et al. 2004). Activation of the pathway from the ventral tegmental area with high-frequency stimulation produces feelings of well-being and results in the avoidance of withdrawal symptoms (Koob 2006). Furthermore, addicts may suffer from dysregulated reward centers (Taghva et al. 2012), predisposing them to relapse (Lubman et al. 2004). Obesity, however, is not always due to an impaired functioning of the reward networks, and brain regions such as the lateral hypothalamus (LH) and ventromedial hypothalamus (VMH) have been shown to modulate feeding behavior and metabolism, in addition to social influences (Halpern et al. 2008). Similarly, in substance dependence, environmental cues associated with substance administration and social aspects may influence drug-seeking behavior (Jentsch and Taylor 1999).

ADDICTION

Preclinical Studies

Preclinical evidence for DBS for addiction stems from animal studies in which DBS of various brain regions results in a reduced self-administration of a variety of substances, including cocaine, alcohol, and opiates. Self-administration of cocaine is reduced in rats after stimulation of the subthalamic nucleus (STN) (Rouaud et al. 2010), NAc (Vassoler et al. 2008), LH, or prefrontal cortex (Levy, Shabat-Simon et al. 2007). Stimulation of the LH and the prefrontal cortex also reduces cue-induced cocaine-seeking behavior. In addition to cocaine, DBS of the NAc has been reported to reduce self-administration of opiates (Liu et al. 2008) and ethanol (Henderson et al. 2010). More recently, bilateral NAc DBS in rats attenuated cue- and heroin-induced reinstatement of drug seeking behavior without long-term influence on physical activity or spatial learning and retention (Guo et al. 2012).

Clinical Studies

Early studies in the surgical treatment of addiction have focused on ablation, cingulotomy (Kanaka and Balasubramaniam 1978), hypothalamotomy (Dieckmann and Schneider 1978; Muller et al. 1973), and resection of the substantia innominata (Knight 1969). In addition, stereotactic ablation of the NAc was further examined for the treatment of heroin addiction in large studies conducted in Russia and China (Gao et al. 2003; Carter et al. 2010). Overall, studies investigating ablation of various targets yielded mixed results likely due in part to interstudy differences in outcome measure, patient population, length of follow-up, and the reporting of side effects, such as cognitive and behavioral effects of ablation (Stelten et al. 2008).

DBS offers several advantages over traditional psychosurgery in that it is less invasive, guided by magnetic resonance imaging, nonablative, and reversible (Glannon 2009). The ability to change stimulation parameters permits the use of sham surgeries and placebo arms in randomized controlled clinical trials evaluating DBS. Follow-up is more likely to occur because of standardization of institutional protocols and the ongoing need for device maintenance. Lastly, a better understanding of the neuropsychological underpinnings of disease has resulted in improved and hypothesis-driven target selection.

Earlier evidence supporting the use of DBS for addiction in humans is derived from case reports of patients with comorbid addictive behaviors who undergo DBS for movement disorders or other conditions. Two patients with Parkinson's disease and comorbid dopamine dysregulation syndrome underwent bilateral STN DBS (Witjas et al. 2005). These patients experienced a substantial reduction in the use of dopaminergic medication postoperatively. Although alleviation of motor symptoms associated with Parkinson's disease alone may explain the decrease in medication usage and addictive behavior, the authors contend that the improvement in behavior may be related to a direct effect of DBS on reward circuits in the brain. Indeed, the role of the STN in the reward pathway is substantiated by advanced magnetic resonance imaging that shows direct STN connections to the medial forebrain bundle (Coenen et al. 2009). However, a study of DBS of either the STN or globus pallidus in Parkinson's disease patients showed that dopamine dysregulation syndrome persisted or worsened in the majority of patients (Lim et al. 2009). More recently, a case report revealed spontaneous remittance of comorbid alcohol dependence in a patient who underwent NAc DBS for a severe anxiety disorder (Kuhn et al. 2007). Following this unexpected finding, five patients with severe and treatment-resistant alcohol addiction have received off-label DBS with the primary goal of improving addictive symptoms. In fact, postoperative alcohol consumption and relapse risk were reduced in all patients (Heinze et al. 2009; Muller et al. 2009). Of these five patients, three patients remained abstinent at 32-month follow-up, one patient had a single short relapse, and the fifth patient still showed a marked reduction of drinking days and drinks per day. While no persistent side effects were observed, all patients reported an absence of craving (Muller et al. 2009). Other investigators have reported smoking cessation among patients who underwent NAc DBS for Tourette syndrome, obsessive compulsive disorder, or an anxiety disorder, although smoking cessation occurred in a minority of the patients (Kuhn et al. 2009). In other case reports of DBS of the NAc in heroin addicts, one subject experienced resolution of his heroin addiction, which persisted for at least 6 years, including after the stimulator was removed (Zhou et al. 2011), and another patient experienced at least 6 months without heroin use, except for a 14-day period of relapse (Valencio-Alfonso et al. 2012). Finally, DBS of the NAc in a patient with severe alcohol addiction was associated with normalization of addictive behavior and craving (Kuhn et al. 2011).

OBESITY

Preclinical Studies

Depending on the target, DBS may induce satiation, decrease appetite, enhance metabolism, or modulate the rewarding aspects of food. The VMH and LH are known satiety and appetite centers in the brain, respectively (Rolls 1984). In early lesioning studies in animals, researchers observed overeating after selective lesioning of the VMH and early satiation after lesioning of the LH (Stricker et al. 1975; Stricker et al. 1978). In more recent DBS studies, high-frequency DBS of the VMH was associated with a moderate increase in food consumption in nonhuman primates (Lacan et al. 2008). In contrast, low-frequency DBS of the VMH inhibited feeding in rats (Krasne 1962), and bilateral LH high-frequency stimulation was associated with a small amount of weight loss likely due to enhanced metabolism (Sani, et al. 2007). The concept of a dual-center theory of appetite regulation

involving the VMH and LH has given way to a more integrated model with a focus on energy expenditure and endocrine signaling of adipose tissue (Sani et al. 2007; King 2006). A more potent determinant of feeding behavior may be related to the palatability or reinforcing value of food, which is modulated by the NAc (Halpern et al. 2008; Teegarden and Bale 2007). In rats, weight loss and decreased hoarding behavior were observed after ablation of dopaminergic input to the NAc; subsequently, levodopa administration resulted in restoration of hoarding behavior (Kelley and Stinus 1985). In another rat study, bilateral DBS of specific subregions of the NAc resulted in differential effects on food consumption and the motivation to work for palatable food (van der Plasse et al. 2012).

Clinical Studies

Indirect clinical evidence for DBS in the treatment of obesity derives from reports of patients experiencing weight loss after DBS treatment intended to target a disease process other than obesity. DBS of the NAc in a patient with treatment-refractory obsessive-compulsive disorder (OCD), nicotine dependence, and obesity resulted in unintended smoking cessation and sustained reduction in food intake with accompanying weight loss (Mantione et al. 2010). As in addiction studies, it is unclear whether resolution of the primary disorder facilitated smoking cessation or weight loss in this patient. Also, weight loss and smoking cessation occurred in a delayed fashion following DBS. Stereotactic electrocoagulation of the LH in obese patients resulted in significant, although transient, appetite suppression and weight reduction (Quaade et al. 1974). Bilateral DBS of the LH was performed in one patient for the primary indication of treating obesity; the patient experienced unintended improvements in memory, although the effect of DBS on weight and food consumption was unclear (Hamani et al. 2008).

LIMITATIONS OF PRECLINICAL AND CLINICAL STUDIES

Evidence from preclinical and clinical studies suggests that DBS may be a potential treatment option for severe and refractory addiction and for several forms of obesity. The level of evidence supporting DBS is primarily observational, however, and no long-term, randomized, blinded clinical trials have been conducted. Several authors call for further research into the mechanism of DBS, potential targets, optimal stimulation parameters, and unanticipated side effects. Attempting to answer these questions using animal models or other human disease states is limited by the models themselves and the inherent neuroanatomical and physiological differences between these conditions.

A limitation in interpreting clinical studies of obesity and addiction relates to heterogeneity of disease within subject populations. For example, craving is part of addiction, and DBS may be associated with reports of an absence of craving; however, different drugs of abuse vary in how much their addictive nature is related to craving (Koob and Volkow 2010). Thus, DBS may be differentially effective for different drugs of abuse. Similarly, obesity varies widely in its underlying pathophysiology, which is likely multifactorial. Several authors have put forth the food addiction model of overeating for obesity. Under this concept, overeating reflects an addictive behavior similar to drug abuse in which individuals are physically and psychologically dependent on foods high in fat and sugar, especially in cases of binge eating

(Smith and Ribbins 2012). Common changes in the brain of substance-dependent and obese individuals further support the concept; these similarities include abnormalities in the dopamine and opioid neurotransmitter systems, changes in fronto-striatal circuitry, and dysfunction of impulsive and compulsive behaviors (Smith 2012). Still, food addiction may only apply to a subset of obese patients, such as those with binge eating disorder (Meule 2011), and many authors have called the food addiction model into question (Ziauddeen et al. 2012; Epstein and Shaham 2010). The complexity and multiple determinants of human feeding behavior and obesity must be appreciated when critically analyzing DBS studies.

A final limitation in interpreting the literature on DBS is publication bias, or the selective reporting of positive outcomes without the reporting of negative results. The field of DBS for mental illness is especially at risk due to its reliance on case reports (Schlaepfer and Fins 2010). Several case reports focus on a secondary outcome, such as memory enhancement after DBS originally intended for weight loss (Hamani and McAndrews 2008). As an additional example, it is unclear whether a patient undergoing DBS for anxiety would have been reported upon had it not been for the observed changes in alcohol use in the patient (Kuhn et al. 2007). Selectively reporting only positive results skews the appearance of truth in regard to a clinical question, which, in turn, could harm patients receiving treatments based on the available evidence. Several researchers call for a comprehensive case registry and qualitative outcome reporting system (Schlaepfer and Fins 2010); however, at the current time, publication bias must be considered when interpreting the literature on DBS.

ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS AND TREATMENT

The future implementation of DBS as a treatment modality for addiction and obesity will involve a risk-benefit analysis, comparing the medical and socioeconomic burden of each disease in a treatment-refractory state to the risks of DBS surgery and its ability to provide symptom resolution. In addition, when framing such an analysis and designing future studies to assess safety and efficacy, ethical issues specific to DBS in patients with addiction and obesity must be considered.

Addiction and obesity are new indications for DBS, which makes a patient agreement to undergo surgery an agreement to participate in a clinical research protocol (Kuhn et al. 2009). Thus, the relationship between health care provider and patient becomes one between investigator and subject, with all associated research subject protections. Under a research protocol, patients must be informed that the expectations of the procedure are not clearly defined.

Patient Selection

DBS for patients with mental disorders has been reserved for those with the most severe and intractable disease. For substance dependence, a determination of severity must take into account the medical effects of the substance of choice, as well as reductions in quality of life associated with the abuse, such as loss of family or occupation. Such social issues are present by definition, as the diagnosis of substance dependence includes continued use despite related problems. Although defining obesity according to BMI may initially make the assessment of the severity of obesity easier, patients show varying degrees of health-

related comorbidities and social difficulties that make an assessment of disease severity more difficult. Another important inclusion criterion is treatment-refractoriness, which includes disease duration and prior failed trials of behavior, pharmacological, and surgical interventions. Finally, further probing into the cause of obesity for a potential subject should be undertaken, as the efficacy of DBS may differ, for instance, for an obese patient with binge eating disorder or one with emotional overeating. Given that the use of NAc DBS for obesity is based on its comparison with addictive behavior, it may theoretically be inappropriate to treat obese individuals with DBS targeting this region who did not display compulsive eating disorders. However, not all individuals exhibiting binge eating behavior are obese and not all obese individuals exhibit binge eating behavior (Ziauddeen et al. 2012), suggesting that further work to elucidate the neuropsychiatric underpinnings of obesity will aid in specific patient selection. Etiologies associated with an alteration in the reward network may be more sensitive to DBS, although future studies are ultimately required for identifying and characterizing this patient population.

Some authors argue that patients with moderate rather than severe disease should be enrolled in small early-phase clinical trials, as moderate disease or disease in early stages may respond better to investigational therapies such as DBS (Kuhn et al. 2009; Espay et al. 2010). For example, neural structures involved in the pathophysiology of a disease may deteriorate over time or as the disease process itself advances. Late-stage or severe addiction involves a devolution of control of behavior from the NAc, which may make intervening on this target less likely to succeed in modulating behavior in this population (Everitt and Robbins 2005). Furthermore, only treating patients with advanced disease, if there is a possibility of increased efficacy of DBS at earlier stages, may represent a violation of justice in that certain individuals would be categorically excluded from a potentially beneficial treatment approach (Kuhn et al. 2009). However, treating patients with substance abuse rather than dependence or attempting to identify patients that may go on to develop a substance-related disorder is challenging. In addition, it is unclear whether certain behaviors will progress to more severe disease or be responsive to treatments less invasive than DBS; instead, such early stages of disease may be more responsive to behavioral interventions. The concept of justice may be invoked more generally in terms of scarce resources and the expense of DBS; however, cost-effectiveness analyses support pursuing further research on DBS for obesity and addiction.

Clinical Trial Design

The reversible nature of DBS allows for prospective, double-blind, randomized, controlled clinical trials, yet it also presents a conflict between achieving the highest research standards and the highest ethical standards (Macklin 1999). Clinical trials conducted for both movement disorders and neuropsychiatric disease have commonly used an “on” versus “off” study design in which all subjects are implanted with DBS electrodes, but only electrodes in a subset of patients are activated, allowing for a comparison between the on and off (or sham surgery) groups (Ackermans et al. 2011; Maciunas et al. 2007) or between groups with a staggered onset of stimulation (Goodman et al. 2010). However, until electrodes are activated in all patients, a subset of patients undergoes the risks of surgery without achieving the immediate potential benefits (Macklin 1999). However, in the case of DBS, sham

surgery is not fully a “sham” in that electrodes are functional and can be activated in a delayed fashion postoperatively.

In addition to comparing groups with and without stimulation, some investigators may wish to assess the effect of DBS alone, without the influence of any other treatment modalities, to avoid confounding factors or to provoke symptoms. Although patients are refractory to current treatment regimens as part of inclusion criteria, discontinuing medication regimens may lead to a worsening or progression of the underlying disorder. In the past, patients experienced negative consequences after medication discontinuation during prior studies of therapeutic agents for mental illness (Hall 1999).

Compensation and Follow-Up

Additional ethical considerations related to study design include compensation for subject participation and follow-up. Despite concerns of funding study enrollment in patients with substance dependence, studies have shown that compensation is not associated with increased relapse rates among study participants (Dempsey et al. 2008). However, excessive amounts of compensation must be avoided, as subjects with addiction may be unduly coerced to participate, especially during times of withdrawal when funds may be applied to purchase substances of abuse. Authors have recommended providing payments to cover time and out-of-pocket expenses related to participation in research, such as time and parking fees (Fry et al. 2006). Denying compensation for involvement in research to individuals with substance dependence would deny the equal distribution of the risks and benefits of participation in research for this population. In addition, such reimbursement improves subject recruitment and long-term follow-up.

Follow-up is important for testing the durability of results over time, yet follow-up and access to care may be limited in patients with addiction (Hall and Carter 2011). Similarly, obesity is more common in socioeconomically disadvantaged populations that may have difficulty with access to care (Saarni et al. 2011). Although several authors call for enrolling subjects with strong family and social support systems, which are essential for influencing a positive outcome (Ford and Kubu 2007), abandoning patients without access to these resources would perpetuate existing disparities. Likewise, financial burden should not prohibit a subject from withdrawing, and all costs of long-term device maintenance should be clearly explained preoperatively.

Several ethical considerations facing subjects enrolled in clinical trials apply to patients undergoing DBS for therapy. The following discussion highlights several ethical issues inherent to DBS treatment of addiction and obesity related to overeating.

Informed Consent and Coercion

As with any invasive procedure, patients must have intact decision-making capacity and must engage in a dialogue with the multidisciplinary health care team regarding expectations and the risks and benefits of the operation (Glannon 2010). However, certain characteristics related to DBS and to addicted and obese patients call into question the integrity of the informed consent process. Patients with severe and intractable disease may be more willing to take on increased levels of risk that are associated with an invasive procedure, especially

after exhausting more conservative treatments, even at an early investigative stage (Hall 2006). Patients' judgment may be clouded by their desperation for a cure and the hype DBS may receive at times in the media and literature (Bell et al. 2011). Although competency and capacity determinations may be more easily made for patients with obesity, patients with substance dependence, by nature of their disorder, may have transient or extended periods of altered consciousness or mental functioning from acute intoxication or withdrawal from a substance, which may preclude them from making informed decisions (Carter et al. 2010). Also, underlying changes and dysfunction of the brain regions controlling reward and decision-making, such as hypofrontality and the lack of top-down inhibitory control, may make addicted patients more likely to take on risky procedures.

As part of the informed consent process, patients must be free of coercion. In legal cases involving substance dependence, individuals in some instances are ordered by the court to undergo drug therapy for addiction (Geppert and Bogenschutz 2009). In other cases, they are offered the option of detoxification as a condition of parole or imprisonment. For example, policies in China and Russia include compulsory detoxification (Orellana 2002; Carter et al. 2010). Should DBS for addiction be determined to be safe and effective, patients may be forced to undergo surgical treatment instead of facing imprisonment. Under such circumstances, patient autonomy would typically be considered violated. Although addicts possess competency, as evidenced by their ability to function in society on a daily basis, competency is not sufficient for autonomy (Caplan 2008). Some authors argue that addicts do not have the capacity to be autonomous because they are limited by their addiction, which coerces behavior (Goodman 1990). In such instances, compulsory treatment may be justified in that the goal of therapy is to relieve the coercion of addiction that threatens patient autonomy (Caplan 2008). Other authors argue that patients have the "right to be sick" and mandatory treatment would violate patient autonomy, regardless of whether the treatment is highly effective in relieving a transiently altered mental state.

Coercion may affect the decision making of obese patients in that they not only face the medical need to lose weight and maintain weight loss, but they may also face discrimination and societal pressures to undergo treatment due to the negative stigma of their disease (Seidell 1998). Indeed, societal pressures may encourage both addicted and obese patients to consent to DBS without full consideration of the risks and benefits. In addition, some patients may enter clinical trials only because such treatment is not otherwise available through routine clinical care. Although these pressures may threaten the informed consent process, the reversibility of DBS empowers the patient and restores some level of autonomy since the patient may choose to turn off or titrate stimulation based on their symptoms at any time. Although reversible compared to ablative surgery, in which there is an intent to destroy tissue, it must be noted to patients that the implantation of DBS may be associated with irreversible complications and significant morbidity in a minority of cases (Boviatsis, Stavrinou et al. 2008).

Patients who are coerced to undergo DBS may not appreciate or have the opportunity to appreciate the risks inherent to the treatment modality. Innate risks, such as hemorrhage associated with device placement, may be overshadowed by the risk driving the coercion. For example, for a patient legally ordered to undergo DBS for addiction, imprisonment

enters into the equation and may overshadow the risk of hemorrhage, a risk that could hypothetically be enough to deter an otherwise noncoerced individual from undergoing DBS. Thus, in a coerced person, the risk–benefit ratio is altered by the nature of the coercion itself.

Enhancement

In addition to targeting the neuropsychiatric underpinnings of disease in patients with addiction or obesity, DBS may have the potential to improve various aspects relating to mood, thought, and behavior in healthy subjects. Should DBS successfully induce weight loss, individuals of normal BMI may request DBS in order to lose additional weight. A key difference in using DBS to treat a nondiseased versus a diseased individual is a change in the risk–benefit ratio. A person suffering from obesity is more likely to receive a greater medical benefit than a person with a normal BMI, although each individual is subject to the same medical risk. Such risks force clinicians to reconsider the ethical notions of beneficence versus non-maleficence. Furthermore, the lower boundary of BMI-defined obesity may easily shift, giving rise to a slippery slope for surgical indications. There are additional risks associated with other enhancing procedures that are tolerated by society, such as liposuction and breast augmentation; however, DBS requires long-term follow-up and the manipulation of nonphysical parameters, which leads to a more complex analysis of risk versus benefit (McGee and Maguire 2007).

There are no systematic studies regarding DBS and improvements in mood, thought, and behavior in healthy subjects; thus, without the ability to judge effectiveness, the risk–benefit ratio cannot be accurately determined. At this time, several authors contend that DBS should be used to restore rather than augment normal function (Synofzik and Schlaepfer 2008). Furthermore, it is unknown whether DBS exerts its effects by disrupting aberrant activity or correcting problems in the regulation of functional circuits (Goodman and Insel 2009). It is therefore unclear whether enhancement can even occur at all with DBS if there is no abnormal neural substrate upon which to act. Nonetheless, a patient undergoing DBS of the LH for the treatment of obesity was noted to show improvements in memory (Hamani et al. 2008). Therefore, although the potential for enhancement would be better determined should further reports of safety and efficacy emerge, unanticipated augmentation of function may occur in patients undergoing DBS for addiction and obesity. Future technological improvements in DBS may also lead to more precise control over targeted areas, increasing both the efficacy of treatment and the pressure for use in augmentation.

Threat to Personhood

The NAc and hypothalamus, proposed stimulation targets in the treatment of addiction and obesity, are also brain regions that control diverse motivational behaviors, and their manipulation may thus lead to varied and unintended effects on mood, thought, and behavior. For example, stereotaxic hypothalamotomy in patients with alcoholism and drug addiction led to improved self-control; however, all patients reported an unanticipated reduction in sexual drive (Dieckmann and Schneider 1978). Similarly, other studies have demonstrated personality changes as unintended consequences after DBS (Bell et al. 2009). Many of these changes are considered side effects of DBS, yet these phenomena are relevant

when discussing personhood (Synofzik and Schlaepfer 2008). In addition to unintended psychological changes, DBS can result in physiological alterations as well. A study of DBS of the NAc and amygdala in heroin addicts showed changes in parameters such as blood pressure and heart rate (Fang et al. 2012).

DBS-induced changes related to the underlying disease pathology can present a further threat to personhood. For obese patients, weight loss results in alterations in body image that can alter one's sense of identity (Sarwer, Wadden et al. 2010). In general, neurosurgical procedures, such as brain tumor resections, may be performed near areas of eloquent cortex, or areas of brain known to serve specific cortical functions such that removal of this brain tissue would directly result in neurological deficits; such deficits may include changes in language, memory, vision, or personality that may alter personhood (Glannon 2009). Many of these changes are tolerated due to an improvement in health related to the primary intervention yet raise ethical issues related to non-maleficence, or doing no harm to the patient. Similarly, a loss or alteration of personhood may be accepted for the resolution of substance dependence or overeating. In fact, some patients believe that treating their underlying disease will allow their true identity to be assumed. Nonetheless, a recent survey of health care professionals revealed acceptance of DBS for psychiatric disease, although a theme that emerged was preservation of personal identity (Mendelsohn et al. 2010).

Manipulation of the Reward Center

An additional threat to personhood is derived from the manipulation of the reward centers of the brain. The feeling of well-being or reward sensation produced by activating the NAc may be altered or deprived in individuals successfully treated by DBS. Perception of reward is an innate characteristic and its artificial modification raises ethical questions regarding the alteration or deprivation of natural pleasure. For instance, a patient undergoing DBS of the NAc primarily for OCD was reported to experience decreased pleasure from the smell and taste of cigarettes (Mantione, van de Brink et al. 2010). Although preventing the sense of pleasure associated with smoking was beneficial to the patient in this particular circumstance, it is unclear whether other innate reward-motivated behaviors might also be altered by DBS, including drinking water in times of thirst, or sexual behavior. In addition, learning new behaviors may be hindered without the positive reinforcement provided by activation of the reward center; however, such concern remains theoretical, as alterations in learning with regard to motivated behavior in association with reward have not been demonstrated at this time (Grubert et al. 2011).

DBS may theoretically yield different clinical results despite identical targets. For example, DBS of the NAc for depression is hypothesized to increase pleasure and reward, yet the same procedure for addiction is believed to reduce the pleasure or reward derived from drugs or food. These observations may be reconciled by viewing neuromodulation through DBS as altering diseased neural networks and circuits, rather than simply altering a brain structure or nucleus in isolation (Grill et al. 2004). Neural networks active in depression and addiction are likely different at baseline and are likely to have differential phenotypes when the same structure within two different networks is activated.

The potential success obtained by targeting the NAc, in terms of treating addiction or overeating associated with obesity, may offset the accompanying potential changes to reward perception. Pleasure has been historically restricted in several instances in order to improve health. For example, the U.S. government sanctioned the removal of trans-saturated fats from fast food in order to help prevent cardiovascular disease, despite what some may argue resulted in diminished taste perception of the resultant food. In the case of DBS, patients will voluntarily decide whether they wish to forgo certain pleasurable experiences in return for treatment of their underlying disease. Furthermore, it is currently unclear whether pleasure from various behaviors will be diminished by DBS. DBS may in fact provide a perception of pleasure that may substitute for the euphoria experienced upon injection of a controlled substance or palatability perceived after ingesting highly caloric food.

MULTIDISCIPLINARY TEAM

Consensus statements generated from conferences on DBS for disorders of mood, thought, and behavior call for multidisciplinary teams to most effectively and ethically implement DBS (Rabins et al. 2009). The success of DBS relies on specialized knowledge possessed by varying individuals that work in close collaboration throughout the treatment course. For example, the psychiatrist/neuropsychologist plays a role in patient selection by assesses a candidate's burden of disease in terms of refractoriness, severity, chronicity, and disability, as well as his or her ability to provide informed consent, freedom from coercion, and presence of support systems. The neurologist/neurosurgeon assesses the patient's medical condition to undergo surgery and discusses the technical risks of the procedure and implanted device. Intra-operatively, the surgeon places the stimulator in an appropriate target with the help of the engineer/neurophysiologist. All teams follow the patient postoperatively. We echo prior guidelines in this area (OCD-DBS Collaborative Group 2002; Nuttin et al. 2003; Fins et al. 2006). An ideal candidate would have disease severe enough to be refractory to conventional therapy yet still maintain decision-making capacity. The patient would undergo DBS at an experienced center with a multidisciplinary team, including an ethics committee overseeing all interventions and reconciling disclosed conflicts of interest. The goal of the procedure should address the pathology identified preoperatively, rather than aim for enhancement, directly or indirectly. A multidisciplinary team ensures that the ethical issues just noted are considered throughout the treatment course. In addition, the presence of various perspectives and individuals provides a system of checks and balances to decrease the likelihood of ethical dilemmas from occurring.

CONCLUSIONS

The success of DBS for movement disorders and the uncovering of the biological basis of mental illness have motivated the expansion of potential DBS indications to the treatment of psychiatric disorders including addiction and obesity due to overeating. These disorders vary greatly but do share similar phenomenology and neurobiology and present specific ethical concerns. In addition to safety and efficacy, ethical considerations related to DBS play a pivotal role in determining the acceptance and subsequent adoption of this technology by both clinicians and society, especially following the notoriety of early psychosurgery. DBS for addiction and obesity is currently investigational, and continued research is warranted.

From an ethical perspective, we support the pursuit of future clinical trials of DBS in a multidisciplinary fashion for the treatment of addiction and obesity. Consideration of ethical issues will provide a framework for neurosurgeons to interpret future advances as indications of DBS for mental illness continue to expand. Multidisciplinary teams consisting of neurosurgeons, neurologists, psychiatrists, psychologists, endocrinologists, bariatric surgeons, ethicists, nurses, nutritionists, and social workers are necessary for the ethical selection and execution of future studies. DBS has been demonstrated to be a powerful tool to address major neurological and psychiatric disease, and it will require an equally robust ethical analysis as it is applied to new areas such as addiction and overeating associated with obesity.

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