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Reversibility and Deep Brain Stimulation

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Abstract
Reversibility is a much-touted advantage of Deep Brain Stimulation (DBS) and related neuromodulatory procedures. In the treatment of both motor and psychological disorders, earlier surgical procedures aimed at the permanent ablation of specific brain areas, but DBS, in contrast, does not deliberately seek to destroy brain tissue. For this and other reasons I discuss, DBS is widely described as "reversible" , and it this claim of reversibility that is the focus of my essay. I argue that, not only is there no common agreement about what "reversibility" means, there are important respects in which the claim is false, and others in which it is misleading.

Keywords
DBS, Deep Brain Stimulation, Psychosurgery, Reversibility, Movement disorders, Neurophilosophy, Neuroethics

> …whilst we think, our brain changes, and that, like the aurora borealis,
> its whole internal equilibrium shifts with every pulse of change.
> —William James, *Principles of Psychology*

Introduction

Reversibility is a much-touted advantage of Deep Brain Stimulation (DBS) and related neuromodulatory procedures. DBS is best known in the treatment of Parkinson Disease and other movement disorders, but recently, researchers have begun to treat a wider array of disorders with DBS, including, more controversially, psychiatric ones. In the treatment of both motor and psychological disorders , earlier surgical proocedures aimed at the permanent ablation of various, targeted brain areas, so the appeal of a neuromodulatory alternative – one which does not deliberately seek to destroy brain tissue – is perhaps obvious. For this and other reasons explored below, DBS is commonly said to be *reversible*.

It is this claim of *reversibility* that is the focus of this critique. Importantly, it is not intended to be a general commentary about the overall therapeutic value of deep brain stimulation nor whether it is an appropriate course of treatment in any given case. These are questions for medical professionals, and highly specialized ones at that, neither of which I am. It is also important to note that some of the disorders and diseases treatable with DBS can be severely painful, disabling, and otherwise intractable; such cases may warrant the risk of irreversible changes or damage to the patient's brain or overall psychological condition. Similarly, Parkinson Disease and some of the other disorders treated with DBS are themselves sufficiently damaging such that the risk not only of permanent changes from the treatment, but the possibility of damage from the disease itself, has to assessed in the context of risks vs. possible gains.

To the extent, however, that contemplation of DBS treatment requires an informed decision on the part of the patient, a more careful analysis of its claims of "reversibility" would seem to be an obvious and integral consideration in the decision process. Unfortunately, the answers to the following questions are anything but clear: What specific aspects or components of DBS are reversible, and what, exactly does "reversible" amount to, in this context? In the context of DBS, *reversibility* enjoys neither universal applicability nor unambiguous understanding.

In what follows I consider various notions of reversibility, examine sample cases of claimed reversibility, and argue that the reversibility of DBS should by no means be taken for granted. Furthermore, the medical uncertainty of the reversibility of both desirable as well as unintended and/or undesirable effects points us toward important and unresolved ethical difficulties concerning DBS. Ongoing controversies concerning its side effects, possible alteration of patients' personalities, mood, cognitive abilities, identities, and sense of autonomy have been widely addressed in the literture, but less attention has been given to the claim that DBS can somehow, reassuringly, all be reversed, and the former controversies only heighten the importance of acknowledging questions of reversibility. Furthermore, as DBS is constantly expanding to new medical applications and likely has not yet realized its full scope or potential, a more thorough appreciation of these questions becomes more significant.

Applications of Deep Brain Stimulation

Although various experimental and diverse methods of electrical brain stimulation can be documented historically, modern DBS is commonly taken to have been in use since 1987 (Ineichen et al. 2014) with the landmark advances of Benabid, et al., in the treatment of Parksonism (Benabid et al. 1987). Since that time, over 100,000 patients worldwide have undergone the procedure. This number is rapidly growing, as is the associated medical research and literature. Since 2000, over 8,000 medical journal articles have been published on DBS since 2000, and over 1,000 have appeared just in the past year (as determined by EBSCO search). DBS is still best known and most commonly used for the treatment of Parkinson's Disease and other movement disorders. These are the earliest modern applications of DBS, and so far, the best understood. They also constitute the only category of applications for which data can be collected about the long-term effects of DBS in a large enough number of patients to be of statistical significance. The ubiquitious claims of reversibility, therefore, may be tacitly resting on these standard sorts of cases which, because of their historical precedence, provide most of the existing clinical data.

In recent years, however, the therapeutic application of DBS has gradually crept into applications involving disorders which, themselves, are not always thoroughly understood, either with respect to the neural mechanisms underlying their manifestation and control, or the diagnostic criteria that identify them. Now, a small but growing number of cases have been treated with DBS for such things as chronic pain, headaches, obsessive compulsive disorder, Tourette Syndrome, severe depression, bipolar disorder and morbid obesity (Dormont et al. 2009). In 2007, DBS was even used in five subjects with writer's cramp that had not responded to other treatments (Fukaya et al. 2007). There is a particularly strong research trend to apply DBS to various psychiatric disorders.

Related to the growing application to psychiatric disorders is a related trend, though one that is still largely still prospective, and that is the treatment of criminal and sociopathic patients with DBS. Perhaps most noteworthy, Italian neurosurgeon Sergio Canavero, has strongly advocated extending various forms of psychosurgery, including DBS and other neuromodulatory procedures to those who engage in criminal or violent behavior and/or who suffer from drug addiction. His recommendations are premised on several controversial assumptions, including that "Free will is a mere illusion", that "Psychopathic behavior is a purely biological epiphenomenon and can be induced", and, with respect to criminal treatment, "The goal is redirecting the action course of the criminal behavior by 'rewriting' the original priming signal to commit an antisocial act" (Canavero 2014). As Canavero is also famous for proclaiming that he will perform the first human head transplant (Canavero 2013), and has attracted criticism on ethical grounds for this (e.g., Kaplan, 2015; Čartolovni and Spagnolo 2015), one should be cautious about regarded his views as representative of mainstream neurology. Nonetheless, the cases he cites as pointing the way toward the treatment of criminal insanity are real, and judging from those and other recent research, there are genuine moves in this direction.

In 2010, for example, a Tulane research team used DBS to treat a nineteen year old woman diagnosed with intermittent explosive disorder. This patient also had been diagnosed with moderate mental retardation and bipolar disorder, and had been treated with various psychotropic medications. She was reported to have tolerated the surgical procedure itself well, but the period of adjusting the neuromodulatory settings took approximately a year, during which the patient was clinically depressed, showed symptoms of obsessive-compulsive disorder, overdosed on her medication and had to be committed to a psychiatric ward for 3 months. After this adjustment period, the authors report that, "the goals of attenuating aggressive impulses and providing the patient with control over her emotions and violent outbursts were achieved. A significant improvement in the quality of life of both the patient and her family was seen almost immediately upon determining the proper settings of her stimulator. … we found that there was a fine line between achieving control of symptoms and producing some depression as well as obsessive-compulsive disorder symptoms" (Maley et al. 2010).

Such applications raise the usual sorts of ethical concerns alluded to earlier, including informed consent, alterations in patient identity, possible restrictions of autonomy, and the need to consider the implications of such surgeries in light of a general, precautionary principle. As noted earlier, these ethical issues have been more widely discussed, and while not the direct concern of this paper, they do make questions about the reversibility of such procedures more compelling.

Claims of Reversibility

One of the chief advantages *claimed* for DBS is that it is *reversible*. Perhaps in the public mind the emphasis of this feature is meant to counter the inevitable specter of past psychosurgical abuses. As noted above, DBS aims toward electrical *stimulation* (neuromodulation), rather than the *irreversible ablation*, of targeted brain tissues. This is in marked contrast with, for example, Walter Freeman's "icepick lobotomies" (in which real icepicks were driven by a hammer through the orbital roof into the frontal lobe), or the crude, early forms of electroconvulsive therapy which were performed without restraints or anaesthetics and produced such violent convulsions that patients' bones and vertebrae often fractured.

Reversibility is also a widely publicized claim in the DBS literature; one finds it in nearly every medical overview, on many patient-oriented websites, and in much of the professional and scientific research on DBS. While DBS has been the focus of ethical concerns, those concerns have largely addressed issues such as safety, patient selection, informed consent, negative psychological side-effects, patient autonomy, personal identity, and its experimental use for psychiatric, and other non-movement related disoders (see, for example, Synofzik, 2015, Clausen, 2010, Schermer 2011). Comparatively little critical attention has been given to the claim of reversibility itself.

In the table below are representative samples of claims of reversibility drawn from sources intended for medical professionals, and also sources meant for patients (the claims of reversibility are unmanageably numerous in the medical and patient literature so this only attempts a small, but reasonable sampling). An examination of these claims shows that, in each case, the nature of the claimed reversibility is subtly different.

The first case is typical for its vagueness; it is the "therapy", non-specifically stated, that is said to be reversible. The second case is more specific, and claims that the "modulation of faulty neural circuits" is reversible, suggesting that those faulty circuits can be returned to their pre-modulated state, or the state they were in before the stimulation was applied. The third claim involves reversing the "functional ablation." In this context, a functional ablation means that the activity of the area targeted by the stimulation is suppressed, so the reversibility claim here suggests that the area will return to a state of pre-stimulation functioning when the suppressing stimulation is stopped. This "functional ablation" stands in sharp contrast with older surgeries that involved the intentional, permanent, physical destruction of brain tissue, and, as noted earlier, it is a contrast many researchers seem particularly concerned to promote.

The fourth claim is similar to the one before, but its target audience is current or prospective DBS patients so may be less technical. What is claimed is a reversible alteration to abnormally functioning brain tissue. The last case, like the former, is meant for the general public consumption. It vaguely, but quite boldly proclaims that "The procedure is entirely reversible, usually with minimal damage to any brain tissue." This seems somewhat contradictory, in that one might wonder how something could be entirely reversible if it causes *any* damage to brain tissue, minimal or otherwise, but perhaps the claim involved here is that the damage to the brain tissue is also reversible. The trouble, of course, is that it is not at all clear what exactly is included within the scope of the term "procedure", so the claim of reversibility is vacuous, if not falsely reassuring. Furthermore, it is a poor basis on which to build an informed patient and medical community.

Claim	Source
1) "Since 1999, the success of deep brain stimulation, a new reversible and adaptable therapy devised for the treatment of Parkinson's disease, has offered the hope of new forms of treatment for patients with severe psychiatric disorders like OCD."	(Medically specialized text) Lévêque, M. 2013. *Psychosurgery: New Techniques for Brain Disorders*. Paris: Springer-Verlag, p. 22.
2) "DBS is appealing because it provides precisely targeted, adjustable, and reversible modulation of faulty neural circuits occurring in a variety of brain disorders."	(Medically specialized text) Marks, WJ. 2015. "Preface." In *Deep Brain Stimulation Management*, 2nd edition, edited by WJ Marks, xi. Cambridge: Cambridge University Press.
3) "Such surgical experiences as reversible functional ablation have been applied to deep brain stimulation (DBS) of thalamus to date, and the most promising surgical target for intractable tremor of PD is the nucleus ventrointermedius (Vim) of the thalamus.	(Medically specialized text) Miyagi, Y. 2015. "Thalamic Stimulation for Parkinson's Disease: Clinical Studies on DBS." In *Deep Brain Stimulation for Neurological Disorders: Theoretical Background and Clinical Application*, edited by T. Itakura, 104. Dordrecht, Netherlands: Springer.
4) "Unlike older lesioning procedures or gamma knife radiosurgery, DBS does not destroy brain tissue. Instead, it reversibly alters the abnormal function of the brain tissue in the region of the stimulating electrode."	(Patient information site) University of Pittsburgh, Neurological Surgery, website for patients: http://www.neurosurgery.pitt.edu/centers-excellence/epilepsy-and-movement-disorders-program/deep-brain-stimulation-movement-disorders
5) "DBS differs from pallidotomy, thalamotomy, and subthalamotomy in that it does not permanently destroy brain tissue. The procedure is entirely reversible, usually with minimal damage to any brain tissue."	(Patient information site) National Parkinson Foundation, patient literature: Okun, MS., and PR. Zeilman. 2014. *Parkinson's Disease: Guide to Deep Brain Stimulation Therapy*. 2nd ed. National Parkinson Foundation, 5. http://www.parkinson.org/sites/default/files/Guide_to_DBS_Stimulation_Therapy.pdf

The next section attempts to further evaluate different aspects of DBS reversibility, but it is in the nature of the problem that perfect clarity is not to be had. In some cases such claims are demonstrably false, in some others likely true, and in some cases, the state of current scientific understanding is not sufficiently developed to know whether such a claim is true. To best examine these questions, however, it is useful to divide the question into two broad categories; reversibility of the implanatation procedure, and reversibility of the effects.

Reversibility and the Implantation Procedure

A current DBS research team puts things succinctly when they say: "DBS has advantages in reversibility and adjustment, but disadvantages in device implantation" (Nishibayashi and Itakura 2015). With respect to the implantation procedure, it is useful to note that the stimulation device consists of three distinct parts: the battery powered pulse generator, or main unit, which is implanted under the skin (usually near the collarbone, though other locations are occasionally used), one or two leads (generally with 4 contacts on each lead) that are inserted into the targeted brain tissue, and a wire that connects the leads to the pulse generator. While procedures for lead placement vary and are in constant development, a common technique involves placement of leads as guided by a rigid stereotactic frame, which is attached to the outside of the patient's head while the patient's brain is imaged by an MRI prior to the to identify the target structures in the brain relative to the frame. In this procedure, the patient is awake during the implantation of the leads (but not in pain), and can give responses to the surgeon to help determine correct lead placement. Recently, results from a variation on this procedure heralded greater accuracy in lead placment, and, in addition to a pre-operative MRI, uses CT scans during the procedure itself, which is conducted on sleeping, rather than alert patients (see Burchiel et al. 2013).

Reports vary about the effects of the lead insertion itself. While many report that this part of the procedure has no lingering effects, neurologist Paul Foley, in a 2015 paper, for example, argues that the mere insertion of the electrodes, can cause irreparable tissue damage, "the long-term consequences of which are unknown" (2015 565). Since detailed, microscopic sectioning and examination of the tissue around the lead cannot happen until post mortem, human data is limited. As with much DBS patient data, reported results vary considerably depending on such factors as the tissues targeted, the disorders being treated, the condition of the patient, duration of the treatment, the clinic at which the surgery is performed, the surgical team, and several other variables.

Most patients, however, show at least some degree of microgliosis; a complex process of localized changes in the glial cells in response to injury. This, too, varies by degree (see, for example, Sun, D.A. et al. 2008).

The issue is more complicated than first appears not only because of the variability and sparseness of results, but because the so-called "microlesioning" of the targeted tissue with the lead itself sometimes provides a noticeable, though temporary, therapeutic contribution, sometimes referred to as the "honeymoon period" (Kumar and Johnson 2011). While techniques are improving every year, in a 2008 text on neural implants generally (including DBS), one researcher summarized the situation as follows:

> It is critical to understand the nature and mechanisms of the tissue response to the implantation, residence, and in the case of stimulation, activation of electrodes in the CNS. These devices are rapidly becoming more widespread, smaller, and more dense. Unfortunately, there remains a lack of first principles understanding of the mechanisms of neuronal injury. Thus, the issue of damaging versus nondamaging neural interfaces has been and will continue to be addressed in a purely empirical manner. Analysis of postmortem human and animal tissue has shown that there is neuronal loss around chronically implanted electrodes and a high density of astrocytes, microglia, and vasculature around the electrode. Loss of neurons around the electrode may affect how well the neural prosthesis functions, especially as devices move toward smaller arrays of electrodes that use microstimulation… (Grill, 2008)

The author further notes that the higher voltages associated with OCD, for example, carry an increased risk of tissue damage.

There is also considerable variation in the number of surgical or device-related complications from one institution to another. A 2006, six year retrospective from Newcastle General Hospital, for example, reports a complication rate of 30%:

> During the study period, a total of 60 patients underwent 96 procedures for implantation of unilateral or bilateral DBS electrodes. The mean follow-up period was 43.7 months (range 6-78 months) from the time of the first procedure. No patients were lost to follow-up or died. Eighteen patients (30%) developed 28 adverse events, requiring 28 electrodes to be replaced. Seven patients developed two adverse

> events and two patients developed three adverse events. The rate of adverse events per electrode-year was 8%. (Paluzzi, et al., 2006). On the other hand, a ten-year retrospective of patients treated at a Swedish hospital, published in 2005, reported only a 15% hardware-related complication rate, and others still lower. (Blomstedt et al. 2005)

In addition to cellular changes surrounding the eletrode, there is, as with any surgery, risk of brain hemorrhage. Estimates vary, but the risk during removal – of concern to the question of reversibility - is greater than during the original implantation. A 2005 retrospective study involving 78 DBS lead removals showed a risk of intracranial hemorrhage of 12.8% per lead for removal, but only 2.0% per lead for implantation (at the authors' clinic). It is important to also point out that, accoding to the authors, "all hemorrhages were asymptomatic" (Liu 2012).

As mentioned previously, the therapeutic value or medical advisability is not the focus here. The concern, rather, is with the frequently touted claim of reversibility, and on this point, the picture appears to be mixed with respect to the implantation of the leads. If reversibility means a return to a state or condition that existed prior to the procedure, the implantation of the leads appears pretty plainly to rule this out. The physical, irreversible changes, one may argue, are of minimal importance, but in some cases, those changes result in permanent, functional changes as well. Moreover, the extent of such changes are variable and unpredictable.

Reversibility and the Effects of DBS

The simplest, and most direct sense in which DBS is commonly taken to be reversible is this: when the current that provides the electical stimulation is stopped, the effects of the current also stop (see, for example, Yu and Neimat 2008; Machado et al. 2012). An examination of the literature, however, shows that this claim, that the effects stop when the current stops, is at best, problematic. Even a cautious defender of DBS points out, that, "While the stimulation might be reversible, it remains an open question to what extent the effects of the stimulation are indeed reversible, and it is the effects which are morally relevant" (Pacholczyk 2015, 641).

For example, with respect to the specific context of DBS's positive effects, one curiously finds discussions involving the *retention of clinical benefit*, rather than reversibility (or irreversibility). Some studies indicate that the therapeutic value of DBS can linger for an indefinite period of time after the neurostimulating current is turned off. One of the earliest reports documenting this longterm effect appeared in 2007 (Hebb et al.) and followed the clinical course a single patient. In a remarkably frank opening statement, the authors write:

> Deep Brain Stimulation (DBS) is an effective treatment option for various movement disorders and is being investigated for use in chronic pain, epilepsy, and select neuropsychiatric conditions. This growing list of indications has superseded our knowledge of either the short- or long-term physiological effects of high frequency stimulation (HFS) in the human brain. Although reversibility is a touted hallmark of DBS, other findings in these patients may allude to more long-term changes taking place in the brain as a result of chronic exposure to HFS. (1958-9)

In the particular patient they followed, the patient was able to stop the stimulation after five years, and was monitored for a year following its cessation. In this patient's case, they speculate as follows: "It is probable that therapy-induced plasticity within the involved circuits contributed to these efffects and further study is needed to discern the physiological sequelae of long-term DBS" (1961). Such study is hampered by the understandable and necessary limitations in studying living subjects. As they explain, "Unfortunately, such studies are difficult or impossible to perform in vivo and there are currently no direct methods of evaluating LTP or LTD [long term potentiation and depression] in the living, in situ human brain" (1961).

Following this 2007 study, some researchers have sought to understand, develop and shape the long term effects of DBS to expand its therapeutic potential. One such article by Ruge, et al., follows another patient with dystonia, in whom "there was no change in average physiological or clinical status when deep brain stimulation was turned off for 2 days, suggesting that deep brain stimulation had produced long-term neural reorganization in the motor system" (2011, 2106-7). Even more recently, a group with the same lead author reported in the *Journal of the Neurological Sciences* that, "during early stages of therapy, dystonia patients often revert back quickly to their pre-operative state when DBS is switched OFF whilst after several years of DBS the beneficial clinical effect in some patients can be retained for long periods" (Ruge et al. 2014, 197-199).

In the kinds of cases described in this section, reversibility may not be desirable since they point to longterm therapeutic value for the patient. Nonetheless, the longterm physiological and changes this research suggests casts further doubt on the idea that DBS can be reversed by simply shutting it off.

Conclusion

I have argued that the claim DBS is reversible is fraught with many difficulties, and at very least, should not be taken for granted. One might claim that the many empirical unknowns and uncertainties in such a new therapy make truly informed consent an impossible epistmological standard. One might also point to the conceptual difficulties of reversibility itself and take the position that *no* mental or physical changes are truly or strictly reversible: *thinking* causes irreversible changes, as William James pointed out over a century ago. These uncertainties and difficulties, however, only underscore the need for greater transparency and candor. The goal of informed patient consent would be better served by replacing the near ubiquitous, over-simplified claims for the reversibility of DBS with a more accurate and better contextualized explanation of changes that may persist indefinitely, and a candid admission of the many uncertainties that accompany them. The extent of these deficiencies points us toward important and unresolved ethical challenges concerning DBS.

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