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How Happy Is Too Happy? Euphoria, Neuroethics, and Deep Brain Stimulation of the Nucleus Accumbens

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Article

How Happy Is Too Happy? Euphoria, Neuroethics, and Deep Brain Stimulation of the Nucleus Accumbens

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Recent studies on deep brain stimulation (DBS) of the nucleus accumbens (NA)—a center of the brain well known to mediate reward, pleasure, and addiction—have provided proof of principle evidence that DBS might be able to induce euphoria in a rapid, well-modulated manner, with potentially much higher efficacy than previous neuropsychiatric interventions. This development evokes two lines of fundamental ethical questions: If happiness were indeed easily inducible by a button press, are there any ethical, psychological, or social limits of DBS-induced happiness? If happiness might be easily inducible not just in persons suffering from psychiatric disease, but also in healthy persons, are there any intrinsic objections against such an enhancement use of DBS? This study uses systematic ethical analysis of recent observations in NA DBS, illustrated by a case vignette and by published reports on other patients. It was found that the benefit of DBS-induced modulation of affective and motivational states comes in degrees: A change in the DBS settings can transform a salutary state of hedonia into a hypomanic or manic state and turn an enhanced affective state into a maladaptive one. Thus, DBS-induced happiness requires an individual, domain-specific functional analysis, which might reveal context-dependent beneficial and detrimental consequences for a person's life. These consequences warrant careful observation of mood states in persons with NA DBS. There are no convincing intrinsic objections against an enhancement use of DBS. However, the lack of evidence about potential benefits, the risk of severe harm, and the high intervention costs currently pose important extrinsic arguments against use of DBS for enhancement purposes.

Keywords: addiction, deep brain stimulation, enhancement, ethics, major depression, obsessive compulsive disorder, psychiatry

“And only the promise of happiness is happiness itself.”
(Nehamas, 2007, 138)

Deep brain stimulation (DBS) of specific brain circuits has been shown to be effective in several treatment-refractory psychiatric diseases (Abelson et al. 2005; Bewernick et al. 2010; Greenberg et al. 2006; Lozano et al. 2008; Mallet et al. 2008; Malone et al. 2009; Nuttin et al. 2003), and the use of DBS for psychiatric indications is rapidly growing (Goodman and Insel 2009). The ventral striatum region and specifically the nucleus accumbens (NA) might function as particularly important psychiatric DBS targets, as treatment effectiveness of these sites has been demonstrated for major depression (Bewernick et al. 2010), obsessive-compulsive disorder (Goodman et al. 2010; Haq et al. 2011; Huff et al. 2010), Tourette's syndrome (Ackermans et al. 2008), anxiety disorders, and substance abuse (Kuhn et al. 2007) (Figure 2). The specific ethical implications of DBS in the ventral striatum/nucleus accumbens, however, have not yet been systematically explored. Here we provide an ethical analysis of recent observations of affective modulation by NA DBS, illustrated by a case vignette and published reports

on other patients. These observations present proof-of-principle evidence that DBS of the brain's “reward system” might rapidly induce smiles and laughter associated with mood elevation, which correlate with voltage increase. These DBS findings compel us to rethink fundamental concepts like happiness and well-being and, in addition, raise fundamental questions about the ethical boundary between therapeutic interventions to relieve symptoms in psychiatric patients (e.g., anhedonia in depression) and enhancement interventions to induce euphoria in healthy persons.

INTRAOPERATIVE EUPHORIA INDUCED BY DBS

A recent study assessed intraoperative DBS-induced mood changes in six patients who received DBS of the anterior limb of the internal capsule and the nucleus accumbens region (ALIC-NA) for treating obsessive compulsive disorder (OCD) (Haq et al. 2011). In five patients, the authors observed a smile that progressed to natural laughter at higher voltages of stimulation. Smiles and laughter were associated with mood elevation, demonstrating that it was not just a DBS-induced facial motor excursion, but indeed an

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expression of a corresponding mental state. For contacts at which smiles and laughter were observed, a positive correlation between voltage and mood was found: The higher the voltage, the stronger was the mood elevation. Mood elevation was not directed at aspects of the environment, indicating that DBS stimulation of the NA induces euphoria rather than context-dependent mirth, which might be mediated by a different brain network (Haq et al. 2011). The dramatic DBS-induced euphoria was expressed by one patient as feeling “happy ... like I won a cruise” (Haq et al. 2011).

These findings confirm several previous observations (Okun et al. 2004; Okun et al. 2007; Springer et al. 2006), and are roughly analogous to psychotropic effects of acute stimulation observed in Parkinson's disease patients with DBS of the subthalamic nucleus (e.g., Chopra et al. 2011; Funkiewiez et al. 2003; Mallet et al. 2007). Yet efficacy of DBS-induced euphoria still seems to be limited: In the aforementioned patients with ALIC-NA DBS, mood elevation during stimulation-induced smiles and laughter was transient, lasting only a few seconds up to some minutes, and habituated with chronic stimulation (Haq et al. 2011; Springer et al. 2006). Future research that is primarily directed at inducing chronic euphoria, however, might be able to identify particularly those DBS locations and parameter settings that lead to *constant* mood elevation. Proof-of-principle evidence for the feasibility of constant mood elevation by DBS is provided by studies in both patients with major depression (Bewernick et al. 2010) and patients with OCD (Goodman

et al. 2010) where DBS of the NA and the ALIC-NA, respectively, led to long-term antidepressant and anti-anhedonic effects.

A CASE VIGNETTE

Our recent observation of a patient treated with NA DBS corroborates the idea that NA DBS might indeed be able to induce both acute and chronic mood elevation even beyond intraoperative settings. A 33-year-old German male diagnosed with combined generalized anxiety disorder (GAD) and obsessive compulsive disorder (OCD) who was implanted with bilateral NA DBS at an outside medical center was admitted to the hospital of one of the authors for internal pulse generator battery exchange and subsequent optimization of parameter settings. To set stimulation parameters, the patient was asked to self-rate three different mood states on a scale from 1 to 10: happiness (0 = feeling completely unhappy, 10 = feeling maximally happy), anxiety (0 = absolutely not anxious; 10 = maximally anxious), and relief from stress and internal tensions (0 = no relief, feeling maximally tense; 10 = absolutely relaxed). Parameter modulation (for details, see Figure 1) revealed two interesting phenomena.

First, the patient reported an increasing sensation of being happy and feeling relaxed in linear correlation to an increment in voltage (see Figure 1). With voltage escalation, he sometimes analogized this experience to the feeling of “getting high” or “being on drugs.” The self-reported

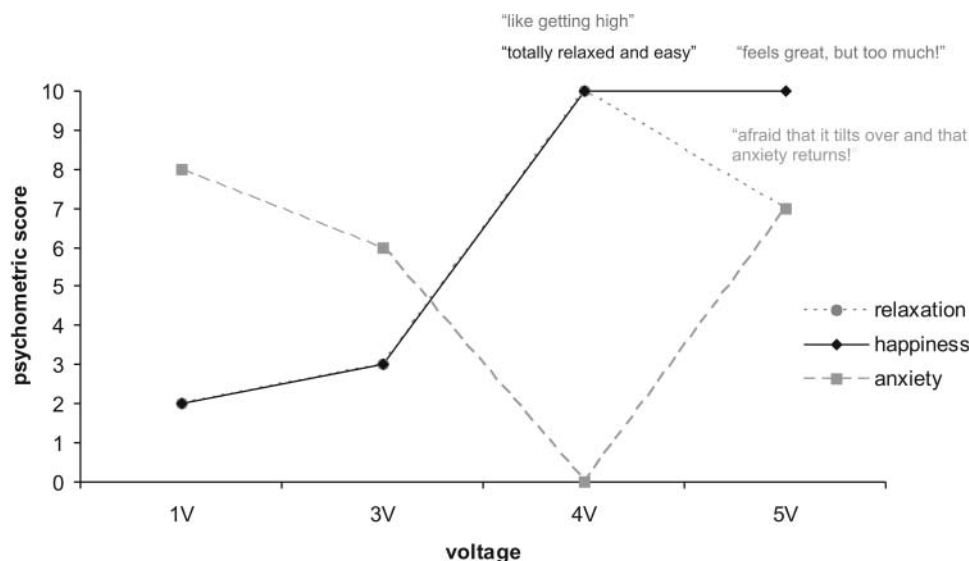


Figure 1. Illustration of the relation between voltage increase and different mood states. The patient reported a linear increase in happiness (continuous black line) and feeling relaxed (gray dotted line) and a decrease in anxiety (gray dashed line) when voltage was increased up to 4 V. A further voltage increase kept happiness at highest levels, but some forms of tension and anxiety reoccurred (psychometric scoring on a 10-point scale: happiness: 0 = completely unhappy, 10 = feeling maximally happy; anxiety: 0 = absolutely not anxious, 10 = maximally anxious; relaxation: 0 = feeling maximally tense; 10 = absolutely relaxed). Only the voltage of left-hemispheric lead was modulated at contact 1; the right-hemispheric lead was held constant at 0 V. Pulse width and frequency were 130 Hz and 120 μ s, respectively, for all testings.

mood improvement corresponded with overt hedonic behavior and a broadening smile. Second, at higher voltages (≥ 5 V) these sensations became excessive or “too much.” The patient began to feel “unrealistically good” and to be “overwhelmed” by the sensations of happiness and ease. He became afraid that the positive effects will “tilt over” and that his “anxiety will come back” (see Figure 1). This second effect might partly correspond to a diffuse, unspecific feeling of overstimulation, which is frequently reported by patients stimulated in different target structures when higher voltages are tested; however, the patient’s statements indicate an additional, more specific experiential quality.

Based on these findings, an intermediate voltage stimulation of 3 V was agreed upon, leaving the patient relatively happy and in a relaxed state, with neither anxiety nor an overwhelming feeling of happiness. The next day, right before discharge, the patient asked to again increase voltage, as he felt that he would like to feel “a bit happier” during the next weeks. After extensive yet difficult deliberation about the benefits of an only intermediate stage of happiness and an intermediate voltage, the parameter settings were left unchanged. Fixed dates for outpatient follow-up visits were arranged before discharge.

DBS AND THE NEUROBIOLOGY OF EUPHORIA

These examples of euphoria—inducible in a rapid and very titratable fashion by a simple linear increase of DBS voltage—certainly provide an only preliminary empirical basis for further ethical discussion. More studies in larger patient groups are required to confirm these effects and study their nature in more detail. Nevertheless, at least in principle, an effect of euphoria induced by NA DBS seems highly plausible based on the fact that the NA is a critical center for the experience of reward and pleasure: Increases in NA neuron activity and dopamine release are observed during expectations and experience of rewards (Adinoff, 2004; de la Fuente-Fernandez et al. 2002; Doyon et al. 2005; Schultz, 2004), and neuroimaging studies have shown increases in ventral striatal activity associated with euphoric responses to dextroamphetamine (Drevets et al. 2001), cocaine-induced euphoria (Breiter et al. 1997), monetary reward (Cohen et al. 2005; Knutson et al. 2001), pleasurable responses to music (Blood and Zatorre 2001), and viewing attractive faces (Aharon et al. 2001).

This “pleasure center” of the brain was first discovered during the 1950s by the psychologists James Olds and Peter Milner. They found that rats would repeatedly press levers up to 2000 times per hour to receive tiny jolts of current injected through electrodes implanted into deep parts of the forebrain. For the sake of this self-induced internal overstimulation, they would stop almost all other normal behaviors, including feeding, drinking, and sex (Olds 1958). This dramatic pleasure-seeking behavior is clearly reminiscent of addiction, as the latter is commonly characterized in exactly this way: a recurring compulsion to engage in some specific activity, despite harmful consequences to one’s well-being (Chou and Narasimhan 2005). Thus, fu-



Figure 2. Lateral x-ray image of two DBS leads in an exemplary patient with DBS to the nucleus accumbens.

ture studies should cautiously monitor whether NA DBS induces or aggravates addiction-like behaviors in at least some patients. Patients who already received NA DBS need to be followed up closely for early detection and possible correction of addictive predilections.

CAN A PERSON BE TOO HAPPY?

If DBS can directly induce happiness and specifically modulate its degree, subjects might ask for a voltage increase even if they seem to be already quite well off. This is exemplified by the case vignette where the patient asked for an increase voltage, as he felt that he would like to feel “a bit happier.” Such requests certainly point to the limits of patient autonomy in requesting an intervention, especially if it involves risks: Physicians are clearly not obligated to change DBS parameter settings beyond established therapeutic levels just because the patient requested it.

However, what are “therapeutic levels” of happiness and are there indeed risks of too high levels of happiness? This raises the complex question of whether happiness always leads to psychosocial well-being and, if not, whether there are optimal levels of happiness. This question is now no longer of only academic interest, but a very practical question, for example, for any psychiatrist who counsels patients with NA DBS and tries to determine the optimal DBS parameters.

To approach this fundamental question we have to ask, first of all, whether the DBS-induced sensations are indeed an expression of some form of happiness. Schematically, two contrary concepts of happiness, each on the edge of a wide conceptual spectrum, can be differentiated in history of philosophy: Aristotle established a materially more demanding notion, according to which happiness (or more precisely, *eudaimonia* rather than *hedonia*; Waterman 2007) consists in the

realization of one's potential (Waterman 1990) or, as defined by most philosophers, in personal flourishing (Bok 2010; Brown 2009; Robinson, 1989). In contrast, Jeremy Bentham proposed a rather formal concept without any further material criteria: Happiness would consist of the presence of pleasure and absence of pain (Burns and Hart 1998). Correspondingly, many contemporary theorists propose either a materially demanding Aristotle-like definition according to which happiness emerges when several specific life conditions are met (such as self-acceptance, environmental mastery, personal growth, and relatedness; Ryan and Deci 2001) or a mere formal definition by defining happiness as the average online experience of pleasure and pain (Kahneman 1999). DBS-induced happiness does certainly not meet the materially demanding notions of happiness: The already-mentioned example of a patient experiencing high levels of euphoria in a probably stressful and wearisome intraoperative setting (Haq et al. 2011) demonstrates that DBS does not induce a type of happiness that depends on mastering certain life and context conditions. This DBS-induced happiness rather comes close to the formal definitions according to which happiness is not much more than net pleasantness. In fact, lay people consider happiness and pleasantness to be conceptually similar, and they usually experience these two emotions together (Oishi et al. 2007). However, it seems most plausible not to equate pleasantness and happiness, but to follow recent psychological multicomponent notions of happiness (Lucas et al. 1996) where pleasant emotions are an important but not exclusive contributory factor to happiness. Other discriminable components like unpleasant emotions, life satisfaction, and domain satisfaction (Lucas et al. 1996) seem to be of similar importance. In other words: DBS-induced pleasantness can largely contribute to, but should not be equated with, happiness.

The question of whether there are optimal levels of happiness, however, needs a functional analysis of happiness in different contexts. This means that we need to acknowledge that happiness (and in particular, mere pleasantness) might not just be an end state that results when things go well, but that it might have context-dependent beneficial and detrimental consequences for a person's life and that these consequences might be ethically relevant when assessing the normative implications of different levels of happiness. In fact, recent studies in psychology found that the optimal level of happiness varies across domains and contexts (Oishi et al. 2007; Ryan and Deci, 2001). For example, although the optimal level of happiness in the domain of volunteer work and in the domain of relationships is the highest possible level of happiness, the optimal level for achievement outcomes—including income and education—is an only a moderate (but not highest) level of happiness (Oishi et al. 2007). These results might be explained by the fact that being only moderately happy allows one to “want more” in one's life, and that this “wanting more” is a major motivation for income, education, and political participation. In particular, the state of being locked into a specific emotion, for example, in constant pleasantness, seems to be dysfunctional as it inhibits flexible adaptation to the highly variable contexts

in which humans are expected to act (Oishi et al. 2007). For example, constant pleasantness might complicate empathy to other persons, prevent necessary efforts to change life circumstances, and impair moral and social decision making (Bodenhausen et al. 1994; Zarinpoush et al. 2000). These arguments suggest that, at least in principle, physicians should discourage an exaggerated level of constant happiness, but allow a rather moderate level of happiness with sufficient freedom degrees for emotional flexibility.

This notion of an optimal moderate level of mood is supported by the observations illustrated in the case vignette: Beyond a certain point, increasing the voltage of the stimulator seemed to transform a salutary state of hedonia into a hypomanic or manic state and to turn an enhanced affective state into a maladaptive one. The patient experienced sensations that became “too much” and began to feel “unrealistically good”; he became afraid that the positive effects would “tilt over.” However, whether a level of happiness is too high, and thus becomes maladaptive, has to be judged on a case-by-case basis.

FEELING A LITTLE BETTER THAN USUAL

The possibility of DBS-induced euphoria also illustrates another fundamental ethical question: If happiness (or at least, pleasantness) can be easily induced by DBS of one's pleasure center, why should we limit its application to treatment of severe, treatment-refractory diseases? For example, in the future, there might be good reasons to use it for enhancing mood states in a patient who does not yet meet the criteria for severe (and even treatment-refractory) disease. Or one might use it to enhance mood states in a patient whose mood states are not affected by the underlying disease per se, such as in an OCD patient showing chronic dysphoria unrelated to OCD. In fact, even affectively and cognitively intact persons without any psychiatric disease might want to use DBS for enhancing their mood. As illustrated by the case vignette, NA DBS might allow such persons to selectively choose stimulation parameters depending on how they want to feel, for example, calm for every day or more “revved up” for a party (Russo 2007). Thus, the enhancement potential of DBS is no longer only speculative in nature and might in fact exceed the enhancement potential of current psychopharmacological substances (de Jongh et al. 2008; Synofzik 2009). But can the use of DBS for enhancement purposes be ethically justified?

Based on the presumption of liberal self-determination, according to which each mentally competent person should at least in principle be free to decide and act according to his or her personal preferences, arguments need to be given in the first place not for *allowing* the use of DBS enhancement, but for *prohibiting* it. Elsewhere, we have argued that enhancing one's cognitive states is not *intrinsically* wrong (Synofzik, 2009; Synofzik and Schlaepfer, 2008). Enhancement by neurotechnologies should—at least in principle—be viewed in the same general category as other means which humans have developed to improve themselves, like education, exercise, information technology, or

nutrition (Greely et al. 2008). These means are certainly not intrinsically unethical. They can be discouraged, however, based on *extrinsic* reasons, such as lack of proven efficacy, safety concerns, or compromising of a person's decisional competencies. Here we show that due to these reasons DBS is not yet ripe for enhancement use.

Lack of Proven Beneficence

Although DBS seems to be efficient in treating anhedonia in a significant share of patients refractory to psychopharmacological treatment (Schlaepfer et al. 2008), there are no systematic studies on the capacity of DBS to enhance mood or cognition in healthy subjects. In particular, we do not yet know whether DBS can induce a constant state of happiness that indeed serves the goals of a person in his/her everyday life. As outlined earlier, even if happiness could be efficiently induced by DBS, it might have detrimental consequences to the person's overall well-being and life satisfaction. In other words, a DBS-induced improvement in one particular state or function (e.g., mood) does not mean that the person is better off (Synofzik and Schlaepfer 2011). Thus, future studies would need to show that an improvement in mood scores indeed translates into an improvement in real-world tasks and in achievement of personal real-life goals (e.g., higher life satisfaction—or *eudaimonia* rather than *hedonia*). But even if such improvements would be shown, there is still one major limitation: Generalized results from DBS studies for enhancement may not always capture the individual patient's experience. Because this experience has an irreducibly subjective element, group studies yielding generalized results will always necessarily be limited in determining this. Thus, as the case for therapeutic DBS mood interventions, the final assessment of the degree of benefit has to be performed on a case-by-case basis also in the case of enhancement DBS.

As it seems unlikely that DBS efficacy studies will be performed in healthy subjects in the near future, current DBS studies in neuropsychiatric patients might be helpful to investigate concomitant DBS effects of enhancing mood and cognition beyond the primary study outcomes. These studies could investigate, for example, whether NA DBS in OCD also improves disease-unrelated mood states, or whether NA DBS in major depression enhances not just anhedonia but also functioning in other neuropsychological domains. A recent study indicates exactly this effect: NA DBS might improve cognition in patients with depression independently from improving the anhedonic component of depression (Schlaepfer et al. unpublished data). Such findings would provide first evidence for the efficacy of DBS to enhance a broader range of neurocognitive capacities unrelated to the primary disease.

Enhancement as a Matter of Degree

As outlined earlier with respect to therapeutic DBS interventions, there are non-linear degrees of benefit of DBS for affective and motivational states. This implies that not only can a therapeutic DBS intervention for pathological con-

ditions shade into enhancement, but also an enhancement DBS intervention can shade into pathology: Too high a level of happiness could be maladaptive. Future studies of DBS for enhancement need to further investigate the continuum of different degrees of happiness in healthy persons, trying to identify whether there are optimal levels of happiness.

Safety Concerns

The not trivial risks of harm in DBS—e.g., bleeding, infection, social misadjustment, or psychosocial changes (Synofzik and Schlaepfer 2011)—will receive much more weight in an enhancement application than in a disease application since it is less likely that they will be outweighed by the likely benefit. In other words, the degree of risks of harm that seems acceptable will depend on the degree of potential benefit. A person suffering from a disease like treatment-resistant major depression is much more likely to receive a positive net benefit from NA DBS than a person who suffers only from some form of melancholy or dysphoria. And, in turn, the risks of side effects like cerebral hemorrhage (Morishita et al. 2010) or addiction-like behavior (discussed earlier) will seem much less acceptable for a mentally intact person than for a person suffering from a severely impaired mental state. Moreover, depending on the stimulation site, DBS might even foil some of the expected enhancement effects, such as by increasing rather than decreasing impulsivity (Frank et al. 2007) or by inducing exaggerated levels of constant happiness that reduce rather than increase psychosocial well-being.

Compromising a Person's Decisional Competencies

The limited knowledge on benefit and risks of DBS for enhancement certainly constrains informed consent and autonomous decision making. This fact, however, applies to many other neuropsychiatric DBS indications as well (Dunn et al. 2011). Other caveats are more specific to the context of DBS enhancement. If DBS induction of chronic euphoria were possible, this experience could change a person's volitions and preferences: He or she might ask for different DBS parameter settings than the treating physicians (exemplified in the case vignette earlier), reject lower voltages or DBS interruption, and engage in other reward-seeking behaviors. These behaviors might be maladaptive for the person. Interruption of DBS might not necessarily lead to cessation of such alterations in volitional behavior: Chronic NA stimulation might alter reward processing (e.g., by DBS-induced neuroplastic changes) in such a way that pleasure experiences and reward expectations are processed differently even *after* DBS interruption. In fact, a DBS interruption might even lead to stronger preferences for restarting and for higher voltages in order to compensate for the transient lack of internal reward stimulation. Thus, in addition to previous skepticism about the alleged "reversibility" of DBS (Synofzik and Schlaepfer 2011), it has to be questioned whether DBS-induced changes to volitional behavior and decisional preferences are indeed reversible in all DBS subjects. The alleged reversibility of DBS—which is still stated

by most authors as one of the main ethical “pro” arguments of DBS (Glannon, 2009; Kringelbach and Aziz, 2009)—might only apply to the *technique*, but not to the *person*.

In addition to volitions and preferences, DBS induction of chronic euphoria could also impair the person’s cognitive capacity to respond to reasons about which volitions and preferences are in his or her best interests. Such an impaired reasoning might likewise not be fully reversible after DBS interruption.

CONCLUSIONS

The potential of DBS to rapidly induce and selectively modulate euphoria evokes deep ethical questions. Its normative evaluation will mainly depend on the context-dependent beneficial and detrimental consequences for a person’s life. These consequences should be carefully studied in those patients who have already received NA DBS.

The use of DBS for enhancement purposes is severely constrained by the lack of evidence about potential benefits, the risk of severe harm, and the risk of altering decisional competencies. An enhancement use of DBS, however, is not intrinsically unethical: If DBS applications will be optimized in a way that it will serve as a highly beneficial, safe, and cost-effective tool in the future, they could be legitimated and maybe even actively endorsed for selected person groups to enhance neurocognitive functioning.

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