

Deep Brain Stimulation to Reward Circuitry Alleviates Anhedonia in Refractory Major Depression

Thomas E Schlaepfer^{*1,2}, Michael X Cohen^{3,4}, Caroline Frick¹, Markus Kosel¹, Daniela Brodesser¹, Nikolai Axmacher³, Alexius Young Joe⁵, Martina Kreft¹, Doris Lenartz⁶ and Volker Sturm⁶

¹Department of Psychiatry and Psychotherapy, University Hospital, Bonn, Germany; ²Departments of Psychiatry and Mental Health, The Johns Hopkins University, Baltimore, MD, USA; ³Department of Epileptology, University Hospital, Bonn, Germany; ⁴Department of Psychology, University of California, Davis, CA, USA; ⁵Department of Nuclear Medicine, University Hospital, Bonn, Germany; ⁶Department of Functional Neurosurgery, University Hospital, Cologne, Germany

Deep brain stimulation (DBS) to different sites allows interfering with dysfunctional network function implicated in major depression. Because a prominent clinical feature of depression is anhedonia—the inability to experience pleasure from previously pleasurable activities—and because there is clear evidence of dysfunctions of the reward system in depression, DBS to the nucleus accumbens might offer a new possibility to target depressive symptomatology in otherwise treatment-resistant depression. Three patients suffering from extremely resistant forms of depression, who did not respond to pharmacotherapy, psychotherapy, and electroconvulsive therapy, were implanted with bilateral DBS electrodes in the nucleus accumbens. Stimulation parameters were modified in a double-blind manner, and clinical ratings were assessed at each modification. Additionally, brain metabolism was assessed 1 week before and 1 week after stimulation onset. Clinical ratings improved in all three patients when the stimulator was on, and worsened in all three patients when the stimulator was turned off. Effects were observable immediately, and no side effects occurred in any of the patients. Using FDG-PET, significant changes in brain metabolism as a function of the stimulation in fronto-striatal networks were observed. No unwanted effects of DBS other than those directly related to the surgical procedure (eg pain at sites of implantation) were observed. Dysfunctions of the reward system—in which the nucleus accumbens is a key structure—are implicated in the neurobiology of major depression and might be responsible for impaired reward processing, as evidenced by the symptom of anhedonia. These preliminary findings suggest that DBS to the nucleus accumbens might be a hypothesis-guided approach for refractory major depression.

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INTRODUCTION

Traditional methods of alleviating depression largely stem from serendipitous observations of antidepressant effects of substances such as iproniazid (originally developed as a treatment for tuberculosis) or imipramine (originally developed as a treatment for schizophrenia). In particular, increasing levels of monoamine neurotransmitters in the synaptic cleft are associated with improvements of depressive symptoms. This insight led to a more targeted drug discovery process, resulting in drugs with fewer side effects, such as SSRIs. These medication treatments, in conjunction with certain methods of psychotherapy and electroconvulsive therapy, are effective at alleviating depressive symptomatology in most patients (Andrews and Nemeroff, 1994; Mann, 2005). However, these treatments do not work for all patients. A sizable minority of patients does not respond. Indeed, twelve percent of patients suffering from major depression have a poor outcome even after 5 years of treatment (Keller *et al*, 1992). Patients who do not respond to any known treatment combination including electroconvulsive therapy are thus referred to as ‘treatment-resistant’ patients, and typically have little hope of recovering.

Psychotropic drugs work by altering neurochemistry to a large extent in widespread regions of the brain, many of which may be unrelated to depression. We believe that more focused, targeted treatment approaches that modulate specific networks in the brain will prove a more effective approach to help treatment-resistant patients. In other words, whereas existing depression treatments approach this disease as a *general* brain dysfunction, a more complete and appropriate treatment will arise from thinking of depression as a dysfunction of specific brain *networks* that mediate mood and reward signals, in particular, the

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*Correspondence: Dr TE Schlaepfer, Department of Psychiatry, University Hospital, Sigmund-Freud-Strasse 25, 53105 Bonn, Germany, Tel: +49 228 287 14715, Fax: +49 228 287 15025, E-mail: schlaepf@jhmi.edu

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cortical–limbic–thalamic–striatal network (Mayberg, 2002). This conceptualization leads to novel ideas about targeted neuromodulatory treatments.

Recent advances in stereotaxic neurosurgical methods have provided a novel and promising technique for alleviating depression in treatment-resistant patients. This technique is deep brain stimulation (DBS), and refers to the stereotaxic placement of unilateral or bilateral electrodes in target brain regions connected to a permanently implanted neurostimulator, which electrically stimulates that brain region (Schlaepfer and Lieb, 2005). Today, DBS is widely used as a treatment for symptoms of Parkinson's disease (Ghika *et al*, 1998; Greenberg and Rezai, 2003; McClelland *et al*, 2005). In these patients, electrodes are placed in the subthalamic nucleus or the globus pallidus internus, and provide immediate recovery to otherwise debilitating motor symptoms. In psychiatric disorders, DBS is used in patients with refractory obsessive–compulsive and Tourette's disorders, and preliminary results suggest that DBS is an effective treatment (Abelson *et al*, 2005; Flaherty *et al*, 2005; Greenberg *et al*, 2003; Gross, 2004; Houeto *et al*, 2005) and stimulation of the nucleus accumbens for this indication has been proposed by one of the authors (Sturm *et al*, 2003). One group has recently reported the use of DBS in patients with major depression (Mayberg *et al*, 2005). In this study, Mayberg and colleagues implanted electrodes in white matter close to subgenual cingulate in Brodmann area 25 (Cg25). Results from this study are preliminary but promising, and open new possibilities for alleviating depression in otherwise treatment-resistant patients. The authors chose Cg25 on the basis of previous findings that this region is implicated in acute induced sadness, is metabolically overactive in treatment-resistant depression, and that clinical improvement after pharmacotherapy and psychotherapy is correlated with decreases in its metabolic activity (Auer *et al*, 2000; Mayberg *et al*, 1999; Mirza *et al*, 2004; Seminowicz *et al*, 2004).

We believe that DBS to the ventral striatum, and in particular, the *nucleus accumbens* (Figure 1), will be a promising and efficacious treatment of severe depression. Our hypothesis is based on three lines of reasoning: (1) the ventral striatum is heavily implicated in both normal and abnormal reward processes, (2) the nucleus accumbens acts as a 'motivation gateway' between limbic systems involved in emotion and systems involved in motor control, and (3) the ventral striatum is uniquely located to modulate activity in other regions of the brain. These arguments are described in detail below.

First, the ventral striatum, and in particular the nucleus accumbens, is a central region for processing reward and pleasure information. Increases in nucleus accumbens 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). Converging evidence of the accumbens' role in reward processing comes from neuroimaging studies, which show 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*, 2001a; O'Doherty *et al*, 2001), pleasurable responses to music (Blood and Zatorre, 2001), and viewing attractive faces

(Aharon *et al*, 2001). Recent evidence demonstrates that the ventral striatum exhibits abnormal activity following administration of dextroamphetamine in patients with major depression, compared with activity observed in healthy control subjects (Tremblay *et al*, 2005). Furthermore, data exploring a specific role of the nucleus accumbens within the limbic system demonstrate that the reward system is dysfunctional in mice submitted to social defeat stress, a dysfunction which is reset by chronic administration of an antidepressant (Berton *et al*, 2006). Together, these findings demonstrate that the nucleus accumbens is a critical center for the experience of reward and pleasure, and that this region is dysfunctional in patients who suffer from depression.

Second, the nucleus accumbens acts as a gateway to transmit, and therefore enhance or degrade, information from emotion centers of the brain to motor control regions of the brain. For example, depleting dopamine from the shell region of the nucleus accumbens in rats severely impairs their ability to engage in reward-seeking behaviors (Ito *et al*, 2004). Human neuroimaging studies have shown that the ventral striatum is very active during reward-seeking behaviors (Juckel *et al*, 2006; Knutson *et al*, 2001b, 2003), and this activation is reduced in certain clinical populations; for example, patients with schizophrenia (Juckel *et al*, 2006). Thus, the nucleus accumbens mediates motivational behavior related to obtaining rewards. This is particularly relevant to the treatment of depression because anhedonia, which can be conceptualized as lack of reward-motivated behavior, is one of the key defining symptoms of the disorder.

Third, the ventral striatum is in a particularly unique position to modulate activity in many other regions of the brain. The nucleus accumbens receives projections from midbrain regions that produce dopamine such as the ventral tegmental area, from regions involved in emotion such as the amygdala, orbitofrontal cortex, and medial prefrontal cortex, from motor regions such as the dorsal caudate and globus pallidus, and from regions involved in memory such as the hippocampus (Nauta and Domesick, 1984). The accumbens in turn indirectly projects to cortical regions including Cg25 and medial prefrontal cortex, the ventral pallidum, the thalamus, amygdala, and hypothalamus (Jones and Mogenson, 1980; Kelley and Stinus, 1984; Mogenson *et al*, 1983). Many of these regions are also implicated in normal and abnormal emotion processing, especially the medial prefrontal cortex and Cg25, suggesting a network of tightly anatomically and functionally connected regions (Mayberg, 1997). These connections can be GABA-ergic (inhibitory) or glutamatergic (excitatory). Thus, stimulating the nucleus accumbens can modulate neural activity in other emotion and motivation centers of the brain. This is further evidenced by our PET data, described below.

Based on this reasoning, we included three patients with severe, treatment-resistant depression to take part in our study on the effects of DBS in the ventral striatum on depression. These patients did not respond to adequate traditional methods including combinations of psychotherapy, psychopharmacological drugs, and electroconvulsive therapy (see Methods). Electrodes were implanted bilaterally in the ventral striatum. Each electrode has four

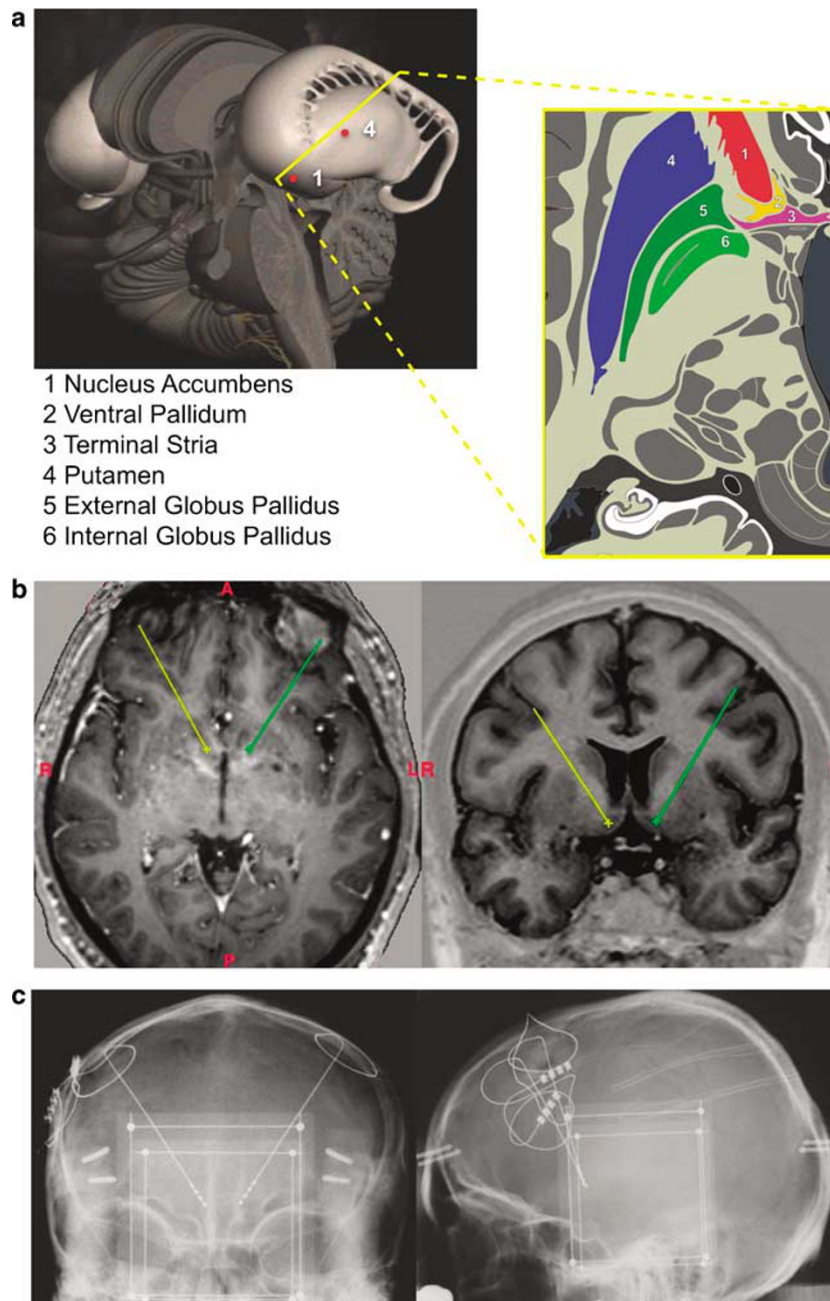


Figure 1 Location of nucleus accumbens and position of deep brain stimulation electrodes. (a) The topographical location of the nucleus accumbens in relation to other brain structures on a horizontal plane 3 mm below the AC-PC plane. (b) The location of the lowest contact of the stimulation electrode in a horizontal and coronal plane with projections of the left (green) and right (yellow) electrode path in the surgical planning stage. Stereotaxic coordinates are 1.5 mm rostral to the anterior edge of the anterior commissure, measured at the crossing point, 4 mm ventral and 7–8 mm lateral of the midline of the third ventricle. Burr holes were placed deep fronto laterally. (c) The actual location of the electrode leads in the post-operative control X-ray.

contacts: (1) the shell and (2) the core regions of the nucleus accumbens, and (3) the ventral and (4) the medial internal capsule (see Figure 2). Electrodes were connected to an automatic stimulator (ie not controllable by the patients), which was implanted subcutaneously over the breast muscle. We report here results of two experiments that demonstrate acute, amelioratory effects on depression as a result of DBS. In the first experiment, we methodically switched stimulation on or off in a double-blind manner over the course of several months and recorded, at each

change, clinical ratings of depression. In the second experiment, we conducted PET scans before stimulation and 1 week after stimulation onset. Results from these two experiments demonstrate that DBS has an unequivocally beneficial effect on symptoms of depression, and suggest that these effects are the result of electrical stimulation of the Nucleus Accumbens, a key structure of the reward system. This is especially striking considering that these patients were not helped by any other treatment methods.

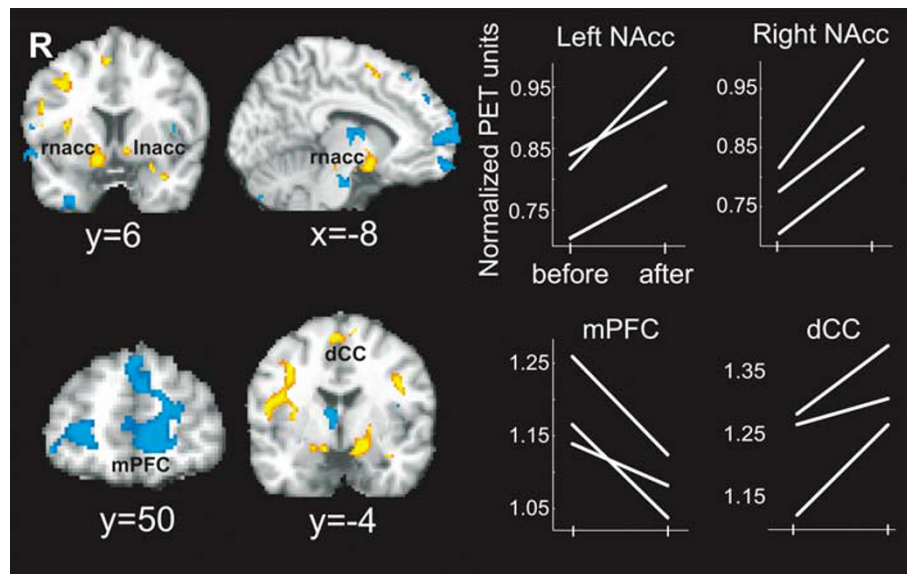


Figure 2 One week after onset of bilateral stimulation to the nucleus accumbens, metabolism in a distributed network of limbic and prefrontal brain regions was altered. Increases in metabolism following stimulation (shown in yellow) were observed in the nucleus accumbens, amygdala, dorsolateral, and dorsomedial prefrontal cortex. Decreases in metabolism (shown in blue) were observed in medial prefrontal cortex and caudate. Graphs on the right display normalized PET units from each subject from before and after implantation in the nucleus accumbens (NAcc), the medial prefrontal cortex (mPFC), and the dorsal cingulate cortex (dCC).

METHODS

We report here on first preliminary results obtained in the first three patients from a investigator initiated double-blinded and placebo controlled study protocol aiming to assess putative effects of bilateral DBS to the nucleus accumbens on depression and quality of life in treatment-refractory patients.

Patients

All patients had in common that they suffered from very treatment-refractory major depression; to be included in the study treatment trials with psychotherapy, pharmacotherapy and ECT had to have failed. From a time point 6 weeks before the study, patients were required to be on stable psychotropic medication, no other concomitant treatment was allowed; throughout the study period reported here medication was continued unchanged.

Patient 01 is a 66-year-old woman suffering from major depression since age 21. The current depression episode was her sixth, and lasted for 17 months. During the current episode, the patient failed seven antidepressant medication trials, and augmentation with five different neuroleptics also failed. The patient did not respond to both an adequate trial of psychotherapy and 13 treatments of bilateral ECT. At study entry the patient was severely depressed, with a Hamilton Depression scale (HDRS₂₄) score of 38. At study entry she was treated with 90 mg duloxetine, 1 mg risperidone, 10 mg diazepam, 75 mg L-thyroxine, and 75 mg melperone.

Patient 02 is a 37-year-old unemployed university graduate (economics). The current episode was his second, and began 9 years ago. Seventeen different antidepressant medication treatments have failed, as did augmentation

with five neuroleptics and lithium. The patient had four courses of unsuccessful ECT treatments with at least 10 treatment sessions (twice unilateral, twice bilateral), and psychotherapy was tried, again to no avail. At study entry he was treated with 50 mg quetiapine and 75 mg amitriptyline.

Patient 03 is the 37-year-old monozygotic twin brother of patient 02; unipolar major depression had developed in both patients in almost exactly the same way at the same time, he had the same professional education and current state as his brother. His current episode began 11 years ago, and this patient has been unsuccessfully treated with at least eight antidepressant medications, and augmentation with at least three neuroleptics and with lithium failed. The patient had two ECT treatment courses (one unilateral and one bilateral), comprising 10 and 15 treatment sessions, respectively, with no success, and psychotherapy also failed. Both brothers (patients 02 and 03) are economics graduates at the university level, but have never been able to work because of onset of their psychiatric illness. They were both living again with their parents in the same household. At study entry they were severely depressed (HDRS₂₄ score of 31 and 32). At study entry he was treated with 50 mg quetiapine, 150 mg amitriptyline, and 75 mg L-thyroxine.

Ethical Considerations

Written informed consent was obtained after all procedures had been explained fully. The ethics committees at the Universities Bonn and Cologne approved this study. In addition, and not stipulated by our ethics committee, an independent psychiatrist (ie not part of our research group) reviewed each patient and clinical data with respect to inclusion and exclusion criteria.

DBS Method

DBS electrode implantation was performed stereotactically; standard Medtronic model 3387 leads were used. This lead has four electrodes over a length of 10.5 mm, each spaced 1.5 mm apart. Intraoperative X-ray was used to verify the positioning of the two electrodes. Only the two lowest of the four contact sites (the lowest one placed in the shell of the nucleus accumbens, the other in its core) of each electrode were used for stimulation. Target-point and trajectory were defined using stereotaxic 3 Tesla MR imaging. DBS treatment was applied with permanent pulse-train stimulation (square-wave impulses of 90 μ s pulse width, 145 Hz and amplitudes of 4 V, electrodes negative against case), those stimulation parameters were chosen because of the extensive experience with neurostimulation for neurological disorders (Deuschl and Bain, 2002; Deuschl *et al*, 2006).

Clinical Ratings

At each study visit, we assessed each patient using over 20 clinical and neuropsychological measures. However, here we limit ourselves to reporting findings obtained from the Hamilton (1960) and Montgomery and Asberg (1979) depression rating scales because these are the most widely used and accepted measures of depression. Nonetheless, findings reported here were consistent across all measures of depression used.

PET Imaging

We acquired two FDG-PET scans from each patient, once 1 week before implantation and once 1 week after stimulation. Before the second FDG-PET examination, patients received stimulation at increasing voltages up to 4 V, 145 Hz during 7 days. Imaging was performed on a PET/CT scanner in 3-D mode (Biograph; Siemens Medical Solutions Inc.) with a 15.8-cm axial field of view and an in-plane spatial resolution of 4.6 mm, according to the procedure guidelines for brain imaging using 18 F-FDG-PET of the European Association of Nuclear Medicine (Bartenstein *et al*, 2002). Blood glucose measured before tracer injection was 96 ± 11 mg/dl. The patients were positioned comfortably in a quiet, dimly lit room several minutes before FDG administration and during the uptake phase of FDG. Scans were performed 30 min after intravenous injection of ~ 200 MBq of 18 F-FDG. The acquisition time was 20 min per position. Low-dose CT for attenuation correction was performed within 1 min before PET administration with the patient in the same position. The acquisition parameters for dual-detector helical CT were 130 kV, 16 mAs, 3-mm slice thickness, and a pitch of 1.2.

Sixty-four slices were acquired (FOV = 332.8, 256×256 Matrix, voxel size = $1.3 \times 1.3 \times 2.43$ mm). Images were normalized into standard space, resampled to 2 mm isotropic voxels, smoothed using a 10 mm FWHM gaussian kernel, and scaled to correct for whole-brain mean differences. Differences in PET values at each voxel between 'before' and 'after' images were assessed using a general linear model in SPM2 with time as the covariate of interest. Non-sphericity due to inherent spatial autocorrelation was corrected for. The resulting t-map was thresholded at

$p < 0.05$ (two-tailed), and a cluster threshold of 50 voxels overlaid on top of a single subject's T1-weighted MRI scan.

RESULTS

Subjective effects were assessed using the morphine-benzodrine group (scores range 0–16) subscale of the Addiction research center inventory, which reflects feelings of euphoria and well-being (Jasinski *et al*, 1984), scores were 0 for all patients for both conditions (stimulation 'on' and 'off'). There were no 'liking' (Kornetsky, 2004) effects during stimulation, in contrast to findings reported by Heath, who observed that human self-stimulation by electrodes in subcortical structures induced extreme rewarding effects (Heath, 1972). Indeed, none of our patients was able to determine whether DBS stimulation was on or off at any time.

Immediate Clinical Effects of Stimulation

Almost immediately (60 s) after switching the stimulation on, one patient was unable to identify any changes, but spontaneously reported that he realized that he was in Cologne, that he never visited the famous Cologne Cathedral, and he planned on doing this in the immediate future, which he indeed did the day following the operation. Asked about depressive symptomatology, he did not report any acute subjective changes. A second patient's immediate (60 s) reaction to stimulation was quite similar; she did not report any acute changes in depressive symptomatology but spontaneously mentioned that she wished to take up bowling again (a favorite pastime of hers 12 years ago, before onset of her depression). She noted, 'This would be quite pleasurable.' These immediate and unprompted behavioral responses demonstrate a sharp increase in exploratory motivation, consistent with the accumbens' role in reward-seeking behaviors. This is especially noteworthy given these patients' severe lack of motivation during their long depressive episode.

Longer Term Clinical Effects of Stimulation

We manipulated the voltage of the stimulation in all three patients in a double-blind manner. Voltage was varied between 0 (eg no stimulation) and 4 V (5 V in the case of patient 2) in 1-V steps. At each change in voltage setting, clinical ratings including the HDRS₂₄ and MADRS were taken. Baseline HDRS₂₄ score was $33.7 (\pm 3.8)$ and baseline MADRS score was $35.7 (\pm 2.9)$, indicating a severe level of depression. The scores dropped significantly to $19.7 (\pm 6.7)$ and $24.7 (\pm 6.7)$ after 1 week of deep brain stimulation (titration period) ($t(2) = 4.68$; $p = 0.02$, and $t(2) = 4.66$; $p = 0.02$). After the first week of double-blind stimulation, the scores dropped to $24.7 (\pm 3)$ ($t(2) = 2.45$; $p = 0.07$) and $26 (\pm 3)$ ($t(2) = 9.67$; $p = 0.04$), respectively. After the first week without stimulation (double-blind), the scores increased again to $29.3 (\pm 5.5)$ and $33.3 (\pm 9.71)$. These ratings in the off-stimulation phase did not differ from baseline ($t(2) = 0.81$; $p = 0.25$ and $t(2) = 0.33$; $p = 0.39$). In addition, we analyzed ratings for single items of both the HDRS₂₄ and the MADRS scale thought to capture aspects of anhedonia, such as 'work and activities' and 'genital symptoms' in the HDRS₂₄ and 'apparent sadness', 'concentration difficulties',

'lassitude', and 'inability to feel' in the MADRS. For none of the items significant changes could be observed (in contrast to the clear and acute clinical changes in anhedonia observed), possibly pointing to limitations of these depression rating scales in assessing the full picture of depressive states. Figure 3 displays clinical ratings as a function of time, and whether stimulation was on or off (gray shading bars indicate that stimulation was on).

Clinical ratings improved in all three patients when the stimulator was on, and worsened in all three patients when the stimulator was turned off. These effects were immediate and bi-directional (eg when the stimulator was turned off, depression ratings immediately worsened, and when the stimulator was turned on, depression ratings immediately improved). The longer term effect on patient 3 is less robust, although despite this immediate two-way effects of stimulation on clinical rating scores could be observed.

We quantified the effects of stimulation on clinical ratings by correlating the ratings (re-coded as percent change from pre-implantation levels to be able to compare across patients and measures) with stimulation parameters. We found a negative correlation (ie increased stimulation led to decreased depression ratings) in all patients for the HDRS₂₄ ($r = -0.73, -0.44, -0.40$) and MADRS ($r = -0.85, -0.36, -0.41$) scores. These correlations were significant across patients (one-sample *t*-test; Hamilton: $t_2 = -5.04, p < 0.01$, MADRS: $t_2 = -3.49, p = 0.03$). Figure 3b illustrates these relationships for both measures and individually for all patients.

Common side effects of depression treatment include agitation, sedation, sleep disturbances, and night sweats. Our patients experienced none of these, and no other negative side effects were observed.

PET Imaging

Statistically comparing 'before' and 'after' stimulation PET scans shows in which regions of the brain did metabolism increase (seen in Figure 2 as orange/yellow) or decrease (blue) across all patients as a function of the stimulation. We observed significant activations (eg greater metabolism following 1 week of stimulation) in bilateral ventral striatum (including the nucleus accumbens), bilateral dorsolateral and dorsomedial prefrontal cortex and cingulate cortex, and bilateral amygdala. Additionally, we observed deactivations (eg decreased metabolism following 1 week of stimulation) in the ventromedial and ventrolateral prefrontal cortex, dorsal caudate nucleus, and thalamus. In order to present the results, we chose the relatively low significance threshold of $p < 0.05$ to see any changes at all in this very small number of patients. See Table 1 for MNI coordinates of all significant changes in metabolism.

Figure 2 additionally displays normalized PET units for each of the three patients in selected brain regions before and after stimulation, demonstrating consistency of the changes in all patients.

DISCUSSION

Bilateral DBS to the nucleus accumbens had immediate effects on ratings of depression in these very treatment-

refractory patients. This was evidenced by both two-way changes in clinical depression ratings and metabolic changes in brain networks associated with depression. This work expands the small but nascent field of the application of DBS for refractory depression by using an hypothesis-driven approach to target a different specific region (Mayberg *et al*, 2005). We selected the nucleus accumbens as a target region because of its prominent involvement in reward and motivation processing and its anatomical connectivity to limbic and prefrontal regions including Cg25. This system is dysfunctional in patients with major depression (Tremblay *et al*, 2005), and a recent study established that social defeat stress in animals lead to alterations of the mesolimbic dopamine system, and interestingly, the behavioral changes in these animals were reset by chronic application of a selective serotonin reuptake inhibitor (Berton *et al*, 2006).

Existing antidepressant treatments focus on combinations of psychotherapy and psychopharmacology. Although psychopharmacological treatments are effective for many patients, they are non-specific in that they significantly alter the neurochemistry of many areas of the brain. This leads to notable side effects that often lead to non-compliance (Keller *et al*, 2002). A more comprehensive conceptualization of depression that inspires specific, targeted neuromodulatory intervention might allow better treatment modalities for depression associated with fewer side effects. Indeed, there were no side effects in any of our DBS patients.

Other brain stimulation techniques exist that use electrical currents or magnetic fields, such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and vagus nerve stimulation, all of which have antidepressant effects (George *et al*, 2000; Schlaepfer and Kosel, 2004; Schlaepfer *et al*, 2003). However, like antidepressants, these methods are also less focused, affect larger areas of the brain not necessarily associated with depression, and induce side effects to various degrees. In contrast, DBS is extremely focused and directly affects only a very small volume of brain tissue.

The effects we describe are acute in all patients. With the onset of stimulation, we observed a significant reduction of ratings of depression, whereas at masked offset ratings of depression increased. Indeed, in patients 2 and 3, this worsening was so bad that the mask had to be broken and they had to be rescued before conclusion of the 4-week masked placebo stimulation period. These two-way changes, observed in masked patients, are a clear indication that the observed results cannot be explained by placebo effects.

Clinical and neurobiological data led to the reintroduction of anhedonia as one of the core symptoms of depression in the DSM-IV in 1994 (Argyropoulos and Nutt, 1997; Rush and Weissenburger, 1994). We hypothesize that our specific treatment modality with a target in the reward system might positively influence this symptom, possibly by restoring normal function of this system. But anhedonia has been implicated with other chronic and debilitating psychiatric disorders such as obsessive-compulsive disorders (Loas, 1996), substance abuse disorders (Wise, 1996), and schizophrenia (Wolf, 2006). These initial observations that DBS to striatal regions indeed might restore dysfunc-

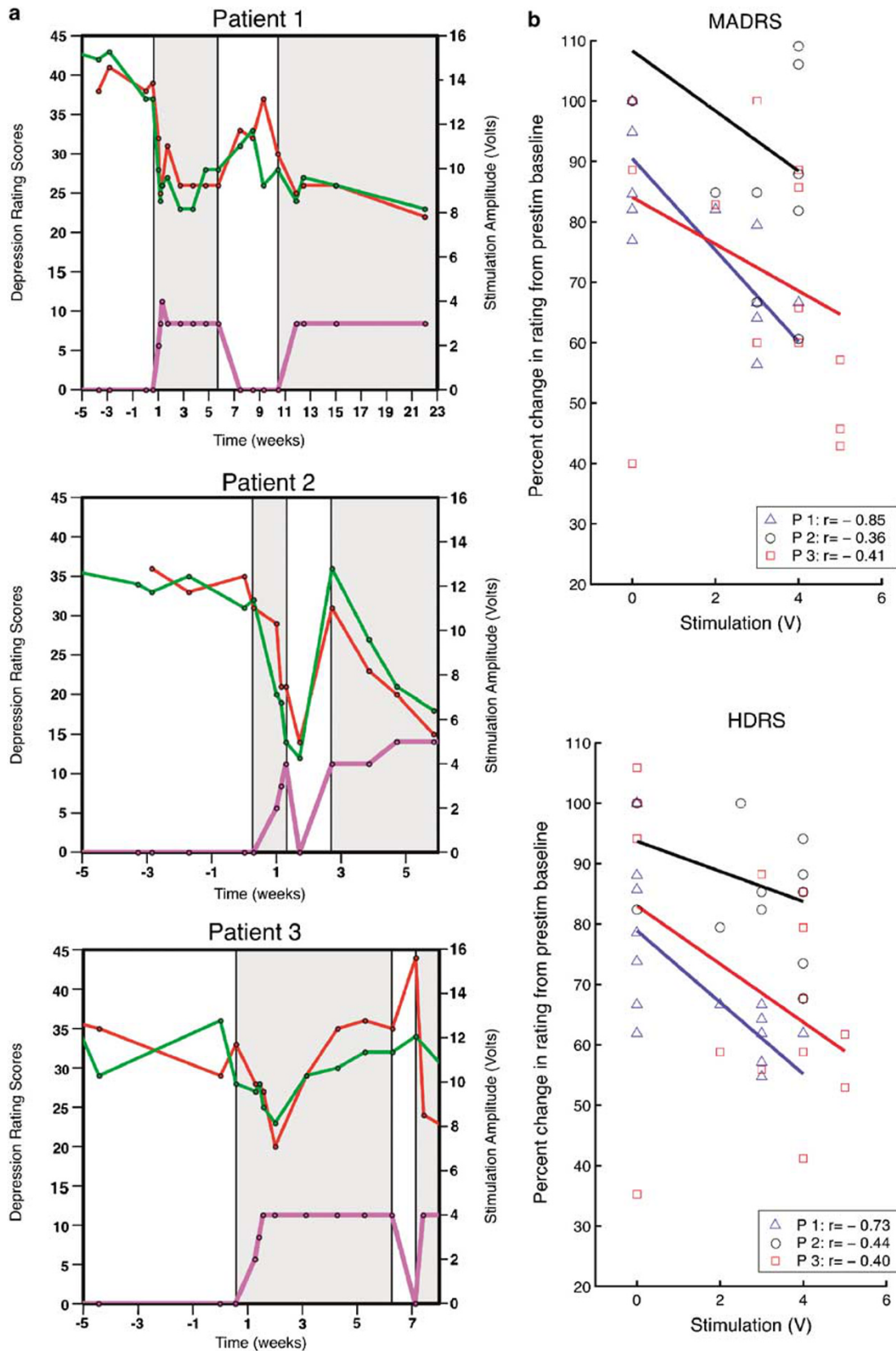


Figure 3 (a) Individual depression score ratings (MADRAS (red) respectively HDRS₂₄ (green)) and deep brain stimulation amplitude (purple) over time for all patients. Gray shading bars indicate stimulation was on. (b) The effects of stimulation on clinical ratings by correlating ratings of MADRAS and HDRS₂₄ re-coded as percent change from pre-implantation levels to be able to compare across patients and measures with stimulation parameters. The figures illustrate these relationships for both measures and individually for all patients.

Table 1 MNI Coordinates and *t*-Values of Maximally Significant Voxels in the PET Contrast of before Stimulation to after 1 Week of Constant Accumbens Stimulation

Region	X, Y, Z (MNI)	t-value
<i>After > before</i>		
L. nucleus accumbens	10, 8, -8	20.90
R. nucleus accumbens	-10, 6, -14	9.41
L. amygdala	14, -6, -18	20.26
R. amygdala	18, -2, -18	6.85
R. middle temporal gyrus	-48, -20, 6	61.75
R. middle frontal gyrus	-52, 4, 20	11.96
L. middle frontal gyrus	44, -14, 34	19.62
R. anterior hippocampus	-28, -22, -16	85.36
L. cerebellum	22, -42, -26	12.60
R. fusiform gyrus	-42, -50, -8	17.70
L. putamen	22, -6, -4	8.77
Superior frontal gyrus	0, -6, 64	15.79
R. angular gyrus	-42, -82, 20	7.49
<i>Before > after</i>		
R. lateral orbital gyrus	-28, 40, -12	-50.89
L. anterior cingulate	12, 50, 0	-26.64
Superior frontal gyrus	-2, 64, 8	-85.36
R. substantia nigra	-6, -22, -24	-43.87
R. inferior frontal gyrus	-36, 42, -4	-22.81
L. anterior insula	38, 14, 4	-27.92
R. thalamus	-4, -6, 8	-9.41
L. caudate	16, 20, 6	-15.79
R. inferior temporal gyrus	-46, -42, -28	-20.26
R. supramarginal gyrus	-58, -40, 38	-14.51

tional processing of reward stimuli lays ground to researching similar approaches for the treatment of those other disorders.

The reported behavioral changes that occurred in these patients beg the question of what neurobiological changes occurred that underlie these behavioral and clinical shifts. Depression is associated with pathological and abnormal functioning of brain regions including striatum and prefrontal cortex. We speculated that DBS to the nucleus accumbens, through its anatomical and functional connections with other limbic and prefrontal structures, would restore activity in these regions to levels seen in non-depressed individuals. This hypothesis is supported by our PET data. One week of DBS significantly increased metabolism in the nucleus accumbens, amygdala, and dorsolateral and dorsomedial prefrontal cortex, and decreased metabolism in the ventral and ventrolateral medial prefrontal cortex. These latter regions have been described to be hypermetabolic in depressed states. In patients with obsessive-compulsive disorder, selective monopolar stimulation of essentially the same target—albeit with a larger single electrode contact—produced acute metabolic effects after 10–20 min that are generally consistent with those found in our study after 1 week of stimulation, supporting

the hypothesis that cortical-thalamic-striatal-cortical circuitry can be modulated by DBS at this target site (Rauch *et al*, 2006). The group of Mayberg *et al* (2005) has demonstrated that improvement of depressive symptomatology in response to different treatment modalities including DBS to it is invariably associated with a metabolic decrease in Brodmann area 25 (Cg25). In our preliminary PET analysis we did not observe significant decreases in Cg25, despite the fact that there are dense monosynaptic projections from this region to the nucleus accumbens. However, it might well be that these decreases in Cg25 might take longer to develop than the short interval of only 1 week between initiation of stimulation and the PET study.

CONCLUSIONS AND LIMITATIONS

These findings should be taken as very preliminary at the clinical level. We certainly do not suggest that DBS to the nucleus accumbens is a ‘magic bullet’ procedure that will cure depression. We and other groups must still demonstrate clinical usefulness of different DBS approaches. However, it is important to note that the patients in this study had severe and long-lasting depression that was not helped by traditional methods. Although DBS to the nucleus accumbens did not ‘cure’ their depression, it remains the only treatment option so far that has minimized levels of depression in many years and many different treatment attempts. This is particularly important because we did not observe any neurological or psychological side effects of this treatment.

Taken together, using a translational approach spanning basic and clinical neuroscience, we found that DBS to brain structures mediating reward and motivation processes has significant, two-way, acute clinical effects on depressive symptomatology. These findings might offer a focused and novel approach to treating refractory major depression with a favorable efficacy to side effect profile.

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Contributions: TS and VS were the study coordinators; TS, VS, and MKo were involved in the protocol design; CF, DB, NA, and MKr were involved in the collection and analysis of data; MC and TS were involved in the statistical analysis, and writing and elaboration of the initial paper. AJ was involved in the analysis of the PET data. DL was involved in the surgical procedures and assessment of patients. All authors reviewed and revised the paper.

CONFLICTS OF INTEREST

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