Published in final edited form as:

Neuroimage. 2011 January ; 54S1: S247–S255. doi:10.1016/j.neuroimage.2010.03.009.

Smile and Laughter Induction and Intraoperative Predictors of Response to Deep Brain Stimulation for Obsessive Compulsive Disorder

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Abstract

We recently treated six patients for OCD utilizing deep brain stimulation (DBS) of the anterior limb of the internal capsule and the nucleus accumbens region (ALIC-NA). We individually tested leads via a scripted intraoperative protocol designed to determine DBS-induced side effects and mood changes. We previously published qualitative data regarding our observations of induced emotional behaviors in our first five subjects. We have now studied these same behaviors in the full cohort of six patients over two years of follow-up and have examined the relationship of these behaviors to intraoperative mood changes and postoperative clinical outcomes.

Five patients experienced at least one smile response during testing. At higher voltages of stimulation some of these smiles progressed to natural laughter. Smiles and laughter were associated with mood elevation. At stimulation locations at which smiles were observed, voltage and mood were significantly correlated ($p=0.0004$ for right brain and $p<0.0001$ for left brain). In contrast, at contacts where smiles were not observed, mood was negatively correlated with voltage ($p=0.0591$ for right brain and $p=0.0086$ for left). Smile and laughter-inducing sites were located relatively medial, posterior, and deep in the ALIC-NA.

The presence of stimulation induced laughter predicted improvement in OCD symptoms at two years. The higher the percentage of laugh conditions experienced in an individual patient, the greater the reduction in YBOCS (24 months, $p=0.034$). Other correlations between clinical outcomes and percent of smile/laugh conditions were not significant. These stimulation-induced behaviors were less frequently observed with one and two-month postoperative test stimulation and were not observed at subsequent test stimulation sessions.

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Intraoperative stimulation-induced laughter may predict long-term OCD response to DBS. Identifying other potential response predictors for OCD will become increasingly important as more patients are implanted with DBS devices. A larger study is needed to better delineate the relationship between induced intraoperative and postoperative emotional behavior and clinical outcome in patients treated with DBS therapy.

Introduction

“Any emotion, if it is sincere, is involuntary.”

Mark Twain

Deep brain stimulation (DBS) is an effective treatment for many neurological diseases, ameliorating select disease features by modulating brain activity. DBS of various brain regions and circuit pathways has been employed to treat many basal ganglia-related disorders (Deuschl et al., 2006; Kumar et al., 2003). DBS has been utilized more recently to treat medication-refractory neuropsychiatric disease (Greenberg et al., 2006; Mayberg HS et al., 2005; Nuttin BJ et al., 2003; Okun et al., 2007).

Intraoperative testing of DBS devices can result in various mood, affective, and behavioral responses of relatively short latency. Smiles (Nuttin BJ et al., 2003; Okun et al., 2004), laughter (Krack et al., 2001), despair (Bejjani et al., 1999), euphoria (Okun et al., 2004), anger (Bejjani et al., 2002), and panic (Rasche et al., 2006; Shapira et al., 2006) have all been observed and reported. The underlying mechanisms may relate to circuit neuromodulation between motor and emotional pathways (Okun et al., 2004), presumably at the interface of the basal ganglia and limbic structures.

We recently completed a six-patient clinical treatment study of medication-refractory obsessive-compulsive disorder (OCD). The study utilized DBS of the anterior limb of the internal capsule and the nucleus accumbens region (ALIC-NA) (Okun et al., 2004; Okun et al., 2007). During intraoperative testing, we observed smiling, laughter, and euphoria in a subset of patients. Understanding the neuroanatomical loci that may underpin these intraoperative phenomena will be critical to a better understanding of neuropsychiatric disease, and to the underlying substrates of human mood and emotion. With its rich connections to frontal, temporal, and hippocampal regions (French and Totterdell, 2002; Roberts et al., 2007), the ALIC-NA is a node for emotional processing. The NA in particular has been closely tied to both pleasure and reward systems. In this report, we analyze relationships between intraoperative stimulation-induced behavior and mood, lead location, voltage/energy delivered, and overall clinical outcome. The purpose of this analysis was to identify predictors of response which can be further examined in future studies.

Materials and Methods

Six subjects with medication-refractory OCD provided informed consent and were enrolled into an IRB-approved NIMH/NIH sponsored study. Two men and four women participated. The mean age of the participants was 36 (range 27 to 54) years and mean time since diagnosis was 22 years (range 10 to 37). To be eligible, documented failure of conventional pharmacotherapy and cognitive behavioral therapy was required (Okun et al., 2007). Details of premorbid psychiatric symptoms in the six patients are summarized in Table 1a.

Each patient received a high resolution volumetric 1.5-Tesla magnetic resonance imaging (MRI) scan on the day prior to surgery. On the morning of the procedure a Cosman-Roberts-Wells head ring was placed on the skull and a computerized tomography (CT) scan performed. These images were fused using in-house created software that is functionally

similar to Varian's ImMerge System (Palo Alto, CA). A deformed three-dimensional subcortical atlas(Sudhyadhom et al., 2009) (based off the Schaltenbrand-Bailey atlas) was employed to determine the target coordinates within a standard coordinate space.

We have previously published details of our surgical implantation procedure(Okun et al., 2007). A 3387-IES DBS lead (Medtronic, Minneapolis, MN) was implanted and utilized for programming and for generating the data for this study. This specialized lead (previously used in some centers for spinal cord stimulation) has four contacts (3 mm long, 4 mm spacing). All implants were bilateral and performed sequentially in a single procedure. Testing was performed after lead targeting and implantation was complete. The right DBS lead was implanted and tested first in each case, followed by the left. The tip of the DBS lead was targeted to pass along the ALIC and approximately through the anterior commissure with the ventral extent to be placed within the nucleus accumbens via methods previously described(Okun et al., 2007; Springer et al., 2006). Single-track Microelectrode Recording (MER) was performed prior to final lead implantation in all cases. During MER we sometimes encountered striatum and accumbens. We relied primarily on the MRI for final lead location (Figure 1).

After implantation each patient underwent videotaped and independent intraoperative test stimulation of each DBS lead (n=12). The leads were separately activated using bipolar settings. After completing testing of the right electrode we tested the left electrode. In accordance with stimulation settings employed by other groups (Abelson et al., 2005; Greenberg et al., 2006; Nuttin et al., 2003) we employed a pulse width (PW) of 210 μ s and a frequency of 135 Hz, with the exception of one patient: subject #4. This patient (with comorbid mild Tourette syndrome) requested "lighter" testing parameters after testing of his right hemisphere. In his case we used a pulse width of 90 μ s (and same stimulation frequency) when testing the left hemisphere.

A single neurologist trained in assessing movement disorders applied test conditions while a psychiatrist assessed changes in OCD, anxiety, and mood at each condition via a ten-point Likert scale. A test condition was defined as the application of a particular voltage at a particular contact. Each contact (0, 1, 2, and 3) of the lead was stimulated intra-operatively at increasing voltages (0, 2, 4, 6, 8V) and turned to zero between each, giving a total of 384 possible test conditions (6 patients $\times$ 2 leads $\times$ 4 contacts $\times$ 8 voltages). If patients could not tolerate a voltage condition, there was no further testing at that contact. In all cases we attempted to move immediately from one test condition to the next and maintained the given stimulation voltage throughout (including at 0V settings). This resulted in an approximate duration at each voltage condition of 30–90s, though this was not standardized, as patient questions or logistical interruptions sometimes led to delays. We tested a total of 308 conditions.

If a smile or laugh was observed, patients were asked to describe their feelings at that moment in time. The assessments were performed for all stimulation conditions. The voltage was reset to zero following each condition and the assessment repeated. Smiles and laughter were recorded if the neurologist and psychiatrist agreed on the observation intraoperatively or, alternatively, on videotape review of these testing sessions (slowing the frame speed to ensure all smiles were captured). Our data analysis excluded all responses other than contralateral smiles and patient-reported Likert-scaled mood and anxiety symptoms. OCD symptoms were rated by patients as 0 in almost every case in the operating room. These scores were therefore excluded.

A MRI-CT fusion 30 days postoperatively confirmed lead positions. The x, y, z coordinates (x=lateral, y=antero-posterior, z=depth, referenced to the mid-commissural point) of the

center of each DBS electrode contact were recorded. This paradigm yielded a total of 48 possible contact locations, of which we tested 46. The most dorsal contact (contact three) could not be examined in patient #1 as she declined to continue intraoperative testing. To yield a set of coordinates normalized for anatomical variability, each patient's lead coordinates were overlaid on a 3-dimensional morph of the Schaltenbrand and Bailey atlas (Sudhyadhom et al., 2009) and their scan morphed to overlap standard anatomical targets. The accuracy of the morph was confirmed by both a neurologist and neurosurgeon.

Patients returned for follow-up visits and data collection at one, two, three, six, 12, and 24 months following DBS device activation. These visits included the measurement of OCD symptoms via the Y-BOCS (Goodman et al., 1989a; Goodman et al., 1989b), and depressive symptoms by the Hamilton Rating Scale for Depression (HAM-D-17) (Hamilton, 1960) both of which we used in our data analysis. Our analyses were divided into assessments of smiling, laughter, mood change, lead location, voltage/energy delivered, and clinical OCD and depression outcome.

Statistical methods

Descriptive statistics were provided for those with stimulation-induced contralateral smiles and those with stimulation-induced laughter. Spearman's correlation coefficients were used to analyze possible relationships between voltage, mood, and anxiety when smiles or laughs occurred (and also in locations of no response). Spearman's correlation coefficients were also used to examine whether a relationship existed between either % smile and % laugh induction (the fraction of a patients' total test stimulations at which an induced smile was seen), Total Energy Delivered (TED, calculated as $\text{voltage}^2 \times \text{pulsewidth} \times \text{frequency} / \text{impedance}$), and one and two year outcomes (as measured by %HAM-D and YBOCS score change). Those with two-tailed p-values less than 0.05 were considered statistically significant.

The clustering of contact locations at which stimulation-induced smiles were observed was statistically examined by calculating the degree to which the mean distance between implicated contact locations deviated from that in a random distribution.

Results

Smile Induction: Initial Characterization

During testing near either the left or right NA, patients reported a sense of euphoria rapidly followed by a smile contralateral to the side of stimulation. The onset of the smile occurred within one to two seconds of stimulation onset in all but one patient (Patient 2), who reported that he had consciously been "trying to keep a straight face". Smiles occurred contralateral to the side of stimulation in all cases. In some cases these progressed to include the bilateral face (4 of 6 patients) and even to natural-sounding laughter (4 of 6 patients, Figure 2). This group of behaviors typically lasted from 45 to 90 seconds, and gradually disappeared during the stimulation period. The mood elevation persisted after the smile/laugh behavior had ceased, but it appeared to end with the termination of the stimulation condition (as judged by patient report and a return to baseline mood scores).

Smile induction was reproducible intraoperatively: when stimulated at the same site and voltage intraoperatively, smiles recurred. This was not always the case at postoperative programming sessions. Each of the 5 patients who displayed a smile response intraoperatively also displayed at least one induced smile response during the first programming visit. However these responses were observed at a smaller percentage of test conditions. Smiles were not typically observed at follow-up visits after the first. We have

previously reported data on Patient 1, in whom stimulation-induced smiling habituated over several months (Springer et al., 2006).

Smile induction: contact location and distribution

Fourteen contact locations on the DBS leads, and 31 voltage settings, resulted in contralateral smiles. Ten smile-inducing contact locations (and 19 voltage conditions) were left-sided and four smile-inducing contacts (12 voltage conditions) were right-sided. Stimulation induced laughter occurred at eight of these contact locations (11 voltage settings). Four of the laughter-inducing contact locations (and 5 voltage conditions) were left-sided and four laughter-inducing locations (6 voltage conditions) were right-sided. Coordinates for these phenomena are provided in Table 2 and depicted in Figure 3. Smiles observed at a specific contact were reproducible intraoperatively. Successive and higher voltage conditions at a 'smile producing contact' resulted in smiles in 31 of 32 data points. Previously, we described an attenuation of smile-response with increasing stimulation voltages (Okun et al., 2004). This attenuation was not consistent within the cohort; several patients showed an increasing degree and duration of effect with increased voltage.

The fourteen lead contact locations that resulted in smiles were clustered ($p=0.035$); i.e. there was a 96.5% or greater chance that the mean distance between smile-producing locations was smaller than in a random distribution. Those lead contact locations on the left that resulted in smiles clustered at a $p=0.020$ significance level while right sided locations clustered at a level of 0.274.

Smile and Mood

Smile responses were mood congruent (mood score > 0) in 28 of 31 smile-producing conditions. Mood scores during stimulation-induced smiles averaged 6.1 (of 10) points, and during stimulation-induced laughter averaged 6.7 points out of 10. By comparison, average patient mood at locations at which patients did not smile was scored at -0.9 points. The mean mood score for conditions which preceded a smile induction was 3.04, and mood elevation preceded smile onset. Mood and anxiety scores in these groups are summarized in Table 1b.

The relationship between patients' mood scores and stimulation voltage was examined in four groups: right and left-sided contacts at which smiles were observed, and right and left-sided contacts at which they were not (Table 3). For contacts at which smiles were observed, the Spearman correlations between voltage and mood were significantly positive ($p=0.0004$ for right brain and $p<0.0001$ for left brain). Voltage and mood were also significantly correlated for the contacts at which stimulation-induced laughter was observed ($p=0.0004$ for right brain and $p<0.0001$ for left). At contacts at which smiles were not observed, the mood was negatively correlated with voltage ($p=0.0591$ for right brain and $p=0.0086$ for left).

Once a patient smiled, further increases in voltage were not correlated with further increases in mood. Voltage was minimally correlated with further mood increase when considering right-sided test sites only (Spearman's $\rho=0.06$), and patients experienced a worsening of mood with left sided locations (Spearman's $\rho=-0.47$). No significant correlation was seen between the minimum voltage at which a smile was observed and the location of the stimulation site.

Smile and clinical outcome

The larger the percentage of laugh conditions for individual patients, the greater the percentage of reduction in YBOCS at 24 month follow-up (Spearman's $\rho=0.841$, p -

value=0.034). The other correlations between clinical outcomes and percent of smile/laugh conditions were not statistically significant (Figure 4). There was no significant correlation observed between the percentage of smile or laugh conditions and TED over the two-year follow-up period. Comparisons between percent of smile/laugh conditions and outcomes, and stimulation settings at follow-up time points, are given in Table 1c and Table 1d respectively.

Discussion

We had not previously quantitatively examined the relationship of the intraoperative smile response to laughter, mood, energy delivered, and outcome in this cohort. Here, we report that subregions of brain in the vicinity of the NA, when modulated by DBS, reliably produced stimulation-dependent mood elevation, smiles, and laughter. The neuroanatomically responsible sites were located medial, posterior, and deep, and clustered in the region close to the accumbens and ventral ALIC.

Treatment Implications

The aforementioned sites produced mood changes when they were transiently stimulated. In this small cohort, intraoperative stimulation-induced laughter predicted long term treatment efficacy in DBS for OCD. The percentage of stimulation conditions that produced laughter strongly correlated with the percentage improvement in OCD symptoms at two years post-implantation and activation (Figure 4). We did not find a significant relationship between the percentage of smiles elicited and OCD improvement. Short term OCD outcomes did not correlate with either intraoperative laughter or smile induction percentages.

One hypothesis to explain our findings is that laughter is an epiphenomenon of stimulation of a putative ‘sweet spot,’ a region which ameliorates OCD symptoms when chronically stimulated. More laughter inductions might indirectly index electrode proximity to this region. It is interesting that the behavioral circuitry of laughter may be impaired in this patient population (Mergl et al., 2003) and that post-medication improvement in OCD symptoms is reported to correlate with normalization of laughter. Mergl and colleagues observed that despite expressing similar levels of amusement, subjects with OCD are moved to laughter more slowly than controls (Mergl et al., 2003). In their study, pretreatment YBOCS scores correlated inversely with subjects’ velocity of laughter and post-treatment OCD remission correlated with a regression in laughter velocity towards normal values (Mergl et al., 2003).

Though laughter might indicate proximity to a putative ‘best implantation target’, it did not predict the ‘best programming contact’ in this small series. Stimulation-induced laughter events failed to correlate with the contact most often employed during follow-up. Based on reports of increased efficacy with ventral stimulation (Greenberg et al., 2006; Nuttin BJ et al., 2003), we typically favored stimulating in a monopolar montage at ventral contacts unless patients experienced psychiatric decompensation or stimulation-induced side effects. Future studies in which programming arrangements are not given *a priori* preference will be required to show whether laughter-inducing contacts are also prime programming contacts. Our current data does not support using the presence of laughter to guide postoperative programming but does offer clues to appropriate intraoperative lead placement.

Stimulation-induced laughter was more likely to be observed either in the operating room or at the first post-operative visit. These effects usually habituated with chronic stimulation. Stimulation-induced smiles have been difficult to induce after one or two months post-surgery. (Greenberg et al., 2006; Springer et al., 2006) If clinicians decide to employ

stimulation-induced laughter to predict OCD improvement it will need to be done soon after device activation.

Reliable, region-specific, transient mood elevation and emotional behavior due to brain stimulation also has implications for the study of the circuitry of mirth and emotion. Acute laughter-like events following focal stimuli have been described during *fou rire prodromique* (Carel et al., 1997), ictal laughter (Arzimanoglou et al., 2003; Oehl et al., 2009), during DBS (Nuttin BJ et al., 2003; Okun et al., 2004), and during cortical stimulation in preparation for epilepsy surgery (Arroyo et al., 1993; Satow et al., 2003; Sperli et al., 2006). Few of these reported events were described as mirthful. A brief sketch of those locations (Figure 5) that are reported to elicit mirthful behavior reveals that they appear to occur primarily within a pyramid defined by the STN, NA, medial temporal cortex (MTC), and hypothalamus (HT). This data fits with current neurological models and the results of functional imaging, which posit pathways for the motor and emotional components of laughter that are initially separate but then merge at the level of the brainstem (Poeck et al., 1963), with the 'emotional laughter' pathway routing through the temporal lobes (Jacome et al., 1980; Oehl et al., 2009) and other limbic aspects of the basal ganglia (Wild et al., 2003). Our observations may provide the following elaboration on this schema: the NAc region appears more closely tied to euphoria rather than context-dependent mirth.

Though previous reports have divided induced laughter into mirthful and mirthless (Wild et al., 2003), we would distinguish the euphoria experienced by patients in our series from reports of context-dependent evoked laughter. We hypothesize that the circuitry underlying euphoria is anterior and medial to the circuitry underlying context dependent mirth. This fits with previous descriptions; for example, Arroyo reported that stimulation of the temporal lobe adjacent to the patient's language center produced amusement at his environment, while more anterior stimulation (in a separate patient) produced euphoric laughter (Arroyo et al., 1993). Similarly, stimulation at the (relatively posterior) STN has been reported to produce amusement at one's environment (Krack et al., 2001), while stimulation of the NA produces euphoria (Di Chiara et al., 2004; Okun et al., 2004; Okun et al., 2007). Though the functions and connections of the accumbens in humans and animals (Bassareo et al., 2002; Roberts et al., 2007; van Dongen et al., 2005) have not been well characterized, the NA is known to be involved in the processing of novelty and reward behaviors (Baldo and Kelley, 2007). The loss of stimulus novelty over time might be hypothesized to be responsible for the response habituation that we observed, but this will require further study. This same circuitry likely plays a role in stimulation-induced phenomena and in our overall positive long-term follow-up. We also found it notable that despite the transient mood elevation seen during stimulation induced smiles and laughter, and despite an overall improvement in depressive symptoms amongst treatment responders (Goodman et al., 2010), improvement in depressive symptoms did not correlate with either smile or laughter percentage in our analysis. The lack of correlation between stimulation induced mood-improvement and sustained improvement in depressive symptoms might indicate that the transient stimulation induced mood response we observed involves different neuronal pathways than those involved in chronic mood changes. This hypothesis will require further investigation.

Limitations

The relatively small number of patients in our series (n=6) increases the chance of error from anatomical and functional variation between patients. Our relatively small sample size may also have left us with insufficient power to evaluate lower amplitude and short-term effects. Further, our patients had refractory OCD and premorbid depression. It is unclear whether our findings are generalizable to patients without OCD. It should be noted that intraoperative stimulations were high current density bipolar montages while monopolar

montages were typically employed for chronic stimulation settings. This may have resulted in greater stimulation spread to surrounding structures in the intraoperative setting than occurred at chronic treatment settings. The circuitry involved in our observations of stimulation-induced laughter may only partially overlap with the circuitry responsible for post-DBS OCD improvement. Finally, future studies in which programming arrangements are not given a priori preference will be required to show whether laughter-inducing contacts are also prime programming contacts. This methodology may have biased our sample data.

Despite these limitations, this pilot study adds to the body of knowledge on pathways responsible for gating emotional reactions. A more detailed examination of the intra-operative smile response, and its potential role as a marker for lead location and therapeutic response, will require a larger sample size for sufficient power to draw firm conclusions. We hope in future studies to verify our results, investigate the response habituation that we observed, and to take up the question of mechanism. Imaging modalities such as Diffusion Tensor Imaging (DTI) and functional Magnetic Resonance Imaging (fMRI) may allow us to examine the overlap between the field of DBS stimulation, white matter pathways, and regions of functional activation.

Acknowledgments

Funding: National Institutes of Health / National Institutes of Mental Health (R21MH064161: *Pilot Study of DBS for Treatment-Refractory OCD* to PI Dr. Wayne Goodman); National Parkinson Foundation Center of Excellence grant.

We thank Karen Klein, MA, ELS (Research Support Core, WFUHS) for her editorial contributions to this manuscript. We are grateful to Anne-Marie Johnson (Creative Commons, WFUHS) and David Peace (Medical Illustration, UFL) for their work on Figures 3 and 5. We also thank Medtronic for donating some replacement DBS electrodes and IPGs (Implanted Pulse Generators) once the primary study had ended. No financial support was provided by Medtronic.

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Figure 1. Sample Lead location and Coordinates

Lead trajectory and contact coordinates for patient 6 based on postoperative CT to preoperative T1-weighted MRI fusion in (A) right coronal, (B) left coronal, (C) right sagittal, and (D) left sagittal views. We employed a 3387-IES Medtronic DBS lead (3 mm long contacts, 4 mm spacing). The tip of the electrode was targeted to pass along the ALIC and approximately through the anterior commissure with the ventral extent to be placed within the NA.

Figure 2.

Patient 6 with a left-sided DBS electrode receiving 6V stimulation. The ventral tip of the electrode was placed in the nucleus accumbens. (A), pre-stimulation. (B) Approximately 1 second after stimulation. (C) 2 seconds after stimulation. (D) Peak facial excursion was reached 3–4 sec after stimulation onset, and laughter continued for another 28 seconds. She continued to smile (bilaterally, and with steadily decreasing amplitude) for another 26 seconds (E), upon which she returned to her emotional baseline (F). The patient denied her mirth was directed at an aspect of her environment and reported feeling “happy... like I won a cruise.”

Figure 3.

Three dimensional and two dimensional distributions of smile and laughter inductions based on postoperative CT to preoperative MRI fusion. Dots represent locations at which unilateral intraoperative post-implantation test stimulation was followed by a smile or laughter. Stimulation-induced smiles occurred at 14 of the 48 different lead locations tested (6 patients X 2 leads X 4 contacts). Stimulation-induced laughter occurred at 8 of the 14 smile-inducing locations. Color coding at each point shows the lowest voltage of induction at that location. Smiles and laughter occurred at lower voltages of induction nearer the target region. The coordinates implicated in left brain stimulation induced smiles were distributed over an area of 2.4cm^3 on the left. Right-brain stimulation smile inductions were distributed over a volume of 0.6cm^3 . Laughter response inducing coordinates were distributed over a volume of 0.6cm^3 on both the right and left. Standard target coordinates for OCD implantation are also depicted for reference (x,y,z= +/-8,12,3, where where x=lateral, y=anteroposterior, z=axial).

	% Smile conditions		% Laugh conditions	
% Improvement	Spearman rho	p-value	Spearman rho	P value
YBOCS at 12 months	0.08571	0.8817	0.34786	0.5295
YBOCS at 24 months	0.65714	0.1724	0.84067	0.0341
HAM-D at 12 months	0.08571	0.8817	0.05798	0.9199
HAM-D at 24 months	-0.25714	0.6487	-0.20292	0.7215
Average TED	-0.48571	0.3582	-0.46382	0.3844

Figure 4. Clinical Outcomes vs Percent of Smile/Laugh Conditions

The clinical variables considered were: OCD symptom burden (YBOCS), Depressive symptom burden (HAM-D), and stimulation field intensity (Total Energy Delivered, or TED, calculated as $\text{voltage}^2 \times \text{pulse width} \times \text{frequency}/\text{impedance}$). Only %laugh reached significance and only at 24 months. As shown above, % laughter did not correlate with % improvement in depressive symptoms at 24 months.

Figure 5.

Most inductions of mirthful laughter have occurred within a pyramid defined by the STN, NA, medial temporal cortex (MTC), and hypothalamus (HT). The figure depicts points at which an inciting event (infarction, seizure, deep brain stimulation, or cortical stimulation) was rapidly followed by laughter, whether with or without mirth. Though hypothalamic loci are not depicted here, both mirthful and mirthless events at the hypothalamus have been reported.

Table 1

Table 1a: Patient Characteristics						
Patient	Age at surgery, gender	OCD age of onset	OCD duration (years)	Baseline HAM-D*	Baseline Y-BOCS*	Principal OCD symptoms and comorbidity**
1	33, F	25	11	6.5	37	Contamination obsession. Washing/cleaning. Avoidance. Anxiety.
2	52, M	17	35	16.5	31	Doubt. Avoidance. Checking.
3	39, M	7	32	12.0	33.5	Doubt. Checking.
4	33, M	7	26	9.5	31.5	Contamination obsession. Comorbid Tourette's.
5	33, F	15	18	12.5	31.5	Contamination obsessions. Avoidance. Anxiety (panic attacks)
6	27, F	5	22	11.5	34.5	Contamination obsessions. Ritualized washing. Counting.

Table 1b: Mean (Range) of Patient Characteristics

	Age	Disease Duration	Baseline YBOCS	Anxiety*	Mood*
Total	36.2 (27–54)	21.7 (10–37)	33.5 (31–38)	3.4 (0–10)	1 (–8–9)
Male	42 (33–54)	27 (20–37)	32.3 (31–34)	3.5 (0–10)	–0.8 (–8–8)
Female	30.3 (27–32)	16.3 (10–22)	34.7 (32–38)	3.3 (0–10)	2.9 (–5–9)
Smile	35.6 (27–54)	22 (10–37)	33.8 (31–38)	3.3 (0–8)	5.2 (–1–9)
Laugh	31 (27–33)	18.3 (10–24)	33.8 (31–38)	3.3 (0–8)	5.3 (0–9)
No smile	39 (39–39)	20 (20–20)	32 (32–32)	3.4 (0–10)	–0.9 (–8–9)
No laugh	46.5 (39–54)	28.5 (20–37)	33 (32–34)	3.4 (0–10)	0.1 (–8–9)

Table 1c: Outcome Scores compared with Percentage of Stimulus induced Behavior

Patient #	YBOCS					HAM-D					Laugh (Y/N)	Smile (Y/N)	*** %age Smile	*** %age Laugh
	Initial*	6 mo	12 mo	24 mo	% Imp**	Initial*	6 mo	12 mo	24 mo	% Imp**				
1	37	14	16	12	67.6	11.5	0	0	16	–39.1	S	S	57.1	20.8
2	31	29	29	32	–3.2	16.5	4	11	12	27.3	N	N	7.1	0
3	33.5	31	7	24	28.4	12	26	4	15	–25.0	N	N	0	0
4	31.5	29	35	30	4.8	9.5	4	22	2	78.9	S	S	6.9	4.2
5	31.5	11	29	21	33.3	12.5	2	10	15	–20.0	S	S	19.4	6.5
6	34.5	2	3	5	85.5	11.5	10	10	7	39.1	S	S	12.5	9.7

Table 1d: Chronic Stimulation Settings									
Patient #	Initial		12 months			24 months			
	Right	Left	Right	Left	Right	Right	Left	Left	
1*	1- C+	6.0V	0- C+	4.0V	1- C+	5.0V	0- C+	4.0V	5.0V
2	1- C+	2.0V	1- C+	2.0V	2- C+	3.5V	2- C+	3.5V	1.5 ^a
3	0- C+	4.0V	0- C+	3.0V	0- 1- C+	7.5V ^b	0- 1- C+	8.5V ^b	8.5V ^b
4	1- C+	2.0V ^a	0- C+	2.0V ^a	1- C+	6.5V ^c	1- C+	6.5V ^c	3.0V ^d
5*	1- C+	3.0V	0- C+	3.0V	0- 1- C+	3.5V	1- C+	3.5V	3.0V
6*	1- C+	4.8V	1- C+	4.8V	1- C+	3.5V ^a	1- 0+	3.3V ^a	3.3V ^a

* Mean of screen and baseline visits.

** All had lifetime history of major depression that was judged secondary to OCD.

* A contact was counted as a 'smile' or 'laughter' location if at least one voltage of stimulation at those coordinates produced a smile or laughter. Mood scores collected during laughter or smile-inducing stimulations tended to be higher than those scores collected at the same location at stimulation settings at which smiles and laughter were not seen. Mean values for smile and laughter stimulations listed in the text are therefore higher than mean values for the location-based 'smile' and 'laughter' groups listed in this table. Mean value calculations also excluded scores obtained during zero-voltage conditions.

* initial scores are an average of baseline and first visit scores

** defined as the percentage of improvement in either YBOCS or HAM-D from initial measurement to 24months

*** defined as the percentage of intraoperative stimulation responses at which a smile or laughter response was seen out of all intraoperative non-zero stimulations

* indicates the patient showed a greater than 33% YBOCS response at 24months

** All patients were stimulated at settings of 135Hz/210µs except for in the following cases: a) 135Hz/90µs; b) 130 Hz/150µs; c) 135 Hz/180µs; d) 60Hz /180µs

Table 2

Voltages Inducing Smiles and Laughter, by Lead Location

Smiles and laughter following left-sided stimulation							
Subject	x (lateral)	y (A-P)	z (axial)	Min V (smile)	Mood (smile)	Min V (laugh)	Mood (laugh)
1	-6.72	14.39	-5.74	2	8		
1	-10.37	17.55	-0.31	4	8		
1	-14.03	20.72	5.13	4	7		
2	-10.28	13.39	-2	6	6		
4	-11.5	13.12	-5.88	6	3	6	3
5	-10.18	9.59	-5.23	6	7	8	9
5	-13.19	12.63	0.19	8	4		
5	-16.19	15.66	5.62	8	5	8	5
5	-19.2	18.71	11.05	8	5		
6	-7.6	12.44	-6.23	6	9	6	9
Smiles and laughter following right-sided stimulation							
Subject	x (lateral)	y (A-P)	z (axial)	Min V (smile)	Mood (smile)	Min V (laugh)	Mood (laugh)
1	8.04	12.41	-6.9	2	8	6	8
1	11.44	16.11	-1.67	4	8	4	8
1	14.84	19.8	3.58	6	8	6	8
6	7.14	12.47	-6.74	6	9	6	9

where x=lateral, y=anteroposterior, z=axial

Mood scored on a 1–10 scale with 10 being most elevated.

The coordinates given represent the locations of those contacts at which smiles were seen. Each contact was stimulated at successively higher voltages (to a maximum of 8V) and the lowest voltages observed to induce smile or laughter responses are listed above. Though smiles were observed at fewer right-sided than left-sided locations, a higher percentage of sites on the right produced laughter with stimulation (100% on the right vs. 40% on the left in the tested voltage range). In all cases, laughter induction required the same or higher voltage of stimulation as smile induction.

Table 3

Correlations Between Emotion Scores and Voltage of Induction

Correlation between mood and voltage at smile vs. no-smile contact locations					
Side	Expression	Number of Locations	Conditions at these Locations	Spearman's rho	p-value
Left	No Smile	13	89	-0.28	0.0086
Left	Smile	10	71	0.69	<.0001
Right	No Smile	19	117	-0.18	0.0591
Right	Smile	4	23	0.68	0.0004
Correlation between mood and voltage at laughter vs. no-laughter contact locations					
Side	Expression	Number of Locations	Conditions at these Locations	Spearman's rho	p-value
Left	No Laugh	19	127	0.02	0.8516
Left	Laugh	4	33	0.75	<.0001
Right	No Laugh	19	117	-0.18	0.0591
Right	Laugh	4	23	0.68	0.0004