LETTERS

Behavioural improvements with thalamic stimulation after severe traumatic brain injury

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Widespread loss of cerebral connectivity is assumed to underlie the failure of brain mechanisms that support communication and goal-directed behaviour following severe traumatic brain injury. Disorders of consciousness that persist for longer than 12 months after severe traumatic brain injury are generally considered to be immutable; no treatment has been shown to accelerate recovery or improve functional outcome in such cases[1,2]. Recent studies have shown unexpected preservation of large-scale cerebral networks in patients in the minimally conscious state (MCS)[3,4], a condition that is characterized by intermittent evidence of awareness of self or the environment[5]. These findings indicate that there might be residual functional capacity in some patients that could be supported by therapeutic interventions. We hypothesize that further recovery in some patients in the MCS is limited by chronic underactivation of potentially recruitable large-scale networks. Here, in a 6-month double-blind alternating crossover study, we show that bilateral deep brain electrical stimulation (DBS) of the central thalamus modulates behavioural responsiveness in a patient who remained in MCS for 6 yr following traumatic brain injury before the intervention. The frequency of specific cognitively mediated behaviours (primary outcome measures) and functional limb control and oral feeding (secondary outcome measures) increased during periods in which DBS was on as compared with periods in which it was off. Logistic regression modelling shows a statistical linkage between the observed functional improvements and recent stimulation history. We interpret the DBS effects as compensating for a loss of arousal regulation that is normally controlled by the frontal lobe in the intact brain. These findings provide evidence that DBS can promote significant late functional recovery from severe traumatic brain injury. Our observations, years after the injury occurred, challenge the existing practice of early treatment discontinuation for patients with only inconsistent interactive behaviours and motivate further research to develop therapeutic interventions.

Severe traumatic brain injury typically results in *en passant* injuries to thalamic and midbrain structures that are essential parts of the forebrain arousal regulation system[6–11]. We sought to determine whether DBS in the central thalamus could promote behavioural responsiveness in a patient in a chronic MCS by approximating the normal role of mesial frontal cortical and brainstem inputs, which adjust firing rates in central thalamic neurons to regulate cognitive effort and maintain brain metabolic activity during normal wakefulness[10,11].

As part of a multi-institutional, FDA- and IRB-approved clinical trial, we implanted DBS electrodes bilaterally within the central thalamus of a 38-yr-old male who remained in an MCS following a severe traumatic brain injury (see Supplementary Information). Over a two-year course of inpatient rehabilitation and four subsequent years in a nursing home, he failed to recover consistent command-following or communication ability and remained non-verbal. Six-and-a-half years after the injury, the patient was re-admitted to an inpatient rehabilitation unit for comprehensive re-evaluation and rehabilitation. Although he remained unable to communicate reliably, functional MRI showed preservation of a large-scale, bihemispheric cerebral language network, indicating that a substrate for further recovery might exist[4]. Additional studies using positron emission tomography showed that the patient's resting global cerebral metabolism was markedly reduced. These observations supported our hypothesis that the patient's inconsistent behavioural responsiveness and communication reflected a global reduction in neuronal activity resulting from widespread de-afferentation and compression injuries to the thalamus and midbrain[4].

We used a single-subject, multiple baseline design to investigate the effects of DBS using a priori statistical evaluation of preselected behavioural metrics. A presurgical baseline established the patient's level of responsiveness before surgery. Post-surgical assessments were conducted within 48 h and during a 2-month period preceding a DBS titration phase in which the patient was exposed to varying patterns of stimulation, to allow us to identify optimal behavioural responses. After the titration phase, a six-month double-blinded crossover phase began, in which DBS was alternated between being turned on and turned off every 30 days (Fig. 1). A multidisciplinary neurorehabilitation team performed all evaluations using standardized assessment procedures.

To assess the effects of DBS, we prospectively chose the JFK Coma Recovery Scale — Revised (CRS-R), a measure of neurobehavioural function that has been validated in patients with disorders of consciousness[12,13] (Supplementary Fig. 1). We also developed three secondary outcome measures that assessed object naming, purposeful upper extremity limb movement and oral feeding to characterize behavioural changes more fully (see Supplementary Information). A comprehensive inpatient rehabilitation program was initiated four months before surgery and continued without modification throughout the study (Figs 1, 2a,b). This program consisted of physical, occupational, speech and recreational therapies and did not differ from the patient's initial course of rehabilitation, which had been completed four years earlier.

CRS-R evaluations conducted over a three-week presurgical baseline verified that the patient's neurobehavioural status was stable. Three subscales of the CRS-R were subsequently selected as the primary outcome measures. Scores on the Arousal subscale indicated that the patient could not consistently respond to basic verbal commands.

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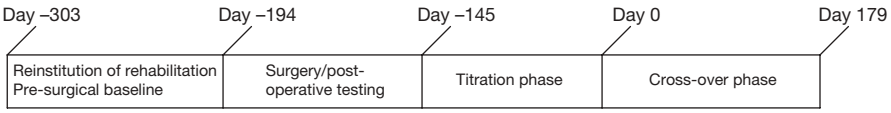

Figure 1 | Study timeline. Timeline illustrating the 483 days of data collection across the different phases of the study.

Motor and Communication scores demonstrated inability to use familiar objects in a purposeful manner or to respond reliably to simple yes/no questions, respectively (Supplementary Table 1).

We then implanted the DBS electrodes, targeting the anterior intralaminar thalamic nuclei and adjacent paralaminar regions of thalamic association nuclei bilaterally (see Supplementary Information). Both electrodes were positioned with each of the four individual contacts within the central lateral nucleus, paralaminar regions of the median dorsalis, and the posterior-medial aspect of the centromedian/parafascicularis nucleus complex. This placement maximized coverage of thalamic regions with strong calbindin protein staining[14]. These calbindin-positive neurons project to supragranular cortical regions[15], consistent with the idea that they have a parallel role in cerebral activation that is comparable to that of projections from the brainstem arousal systems[16].

We evaluated electrical stimulation at each electrode contact within 48 h of surgery to identify potential adverse effects and to determine voltage thresholds for behavioural changes. Stimulation produced acute changes in arousal including increased heart rate, well-sustained eye opening and rapid bilateral head-turning to a voice[17]. Such effects were observed for all electrode contacts tested, and each electrode had a preferred contact with the lowest voltage threshold for eliciting a response. We further determined a specific configuration of electrode cathode/anode geometries (monopolar versus bipolar) for each electrode that minimized this voltage threshold. We assessed behaviours over 20–30-min periods of bilateral DBS that alternated between on and off. During object naming, speech remained unintelligible and was limited to episodes of incomprehensible word-mouthing. The frequency of limb movements that involved social gesture and object use was significantly higher with DBS on than with it off (Supplementary Table 2), although we never observed fully executed movement sequences. On post-operative day 2, we recorded cortical potentials evoked by electrical stimuli delivered to the individual contacts of each DBS lead using time-locked averaging of the scalp EEG (Supplementary Fig. 7). The total exposure to DBS during this phase was approximately 2 h, and there was no further exposure to DBS for the next 2 months (Fig. 2b).

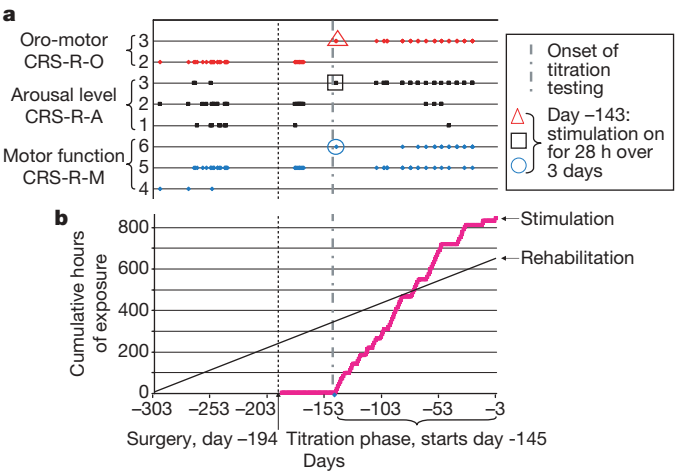

Figure 2 | Qualitative changes in behaviour on CRS-R subscales associated with titration phase and cumulative hours of rehabilitation and brain stimulation. a, The CRS-R subscale scores are shown from enrolment (Day –309) to the end of the titration phase (Day –1). Abrupt changes in CRS-R subscale scores were seen after the onset of the titration phase (Day –145). **b**, Cumulative hours of rehabilitation and electrical brain stimulation are shown across the same time period. Exposure to rehabilitation hours is constant at 3 h per day, 5 days per week (estimated as 660 h over 44 weeks, black line). The accumulation of hours of continuous stimulation is shown in magenta.

The titration phase began 50 days after surgery (Figs 1, 2b) and continued for 18 weeks. The CRS-R, object naming and limb movement protocols were administered weekly to test a range of different stimulation frequencies (70–250 Hz) and intensities (0–5 V). The duration of alternating time on and off stimulation was gradually increased from three to fourteen days. The frequency range explored was guided by ongoing empirical observations of the patient and previous results in primate and rodent experiments that showed behavioural facilitation by stimulation of the central thalamus using frequencies of 50–100 Hz[18,19].

We noted several qualitative changes in behaviour during DBS titration that correlated with abrupt changes in CRS-R subscale scores (Fig. 2a). These changes were observed shortly after the onset of continuous bilateral stimulation on day –145 (Fig. 2b). Longer periods of eye opening and increased responsiveness to command were reflected in increased CRS-R Arousal scores. On day –143, the patient showed the first instances of functional object use on the Motor subscale (score = 6) and intelligible verbalization on the Oromotor subscale (score = 3). No previous episodes of intelligible verbalization had been observed during a series of 33 evaluations conducted across the first 6 months of observation. These behavioural improvements (and other improvements, see Supplementary Information) temporally coincided with the onset of DBS (Fig. 2a) and did not emerge until 160 days after initiation of the rehabilitation program, indicating that they were primarily attributable to the DBS.

After titration testing, we chose a final set of stimulation parameters for each electrode (100 Hz, right side–bipolar field, 4 V; left side–monopolar field, 4 V), reflecting considerations of behavioural observations and of battery life. The patient then began the crossover phase. Data were collected daily by the same team that performed the baseline assessments. Comparison of the DBS on and off conditions showed that the patient received the maximal score on the Arousal subscale significantly more often during the DBS-on periods (Fig. 3; $P < 0.001$, Pearson Chi-square (two-tail), Systat). There was no significant difference in performance on the CRS-R Motor and Communication subscale scores throughout the crossover phase, probably reflecting a ceiling effect on both subscales. The patient's ability to execute complete functional limb movement sequences (for example, bringing a cup to his mouth) also significantly improved with DBS on ($P < 0.001$, Pearson Chi-square (two-tail), Systat), as did his ability independently to chew and swallow a bolus of food placed on his tongue (Fig. 3; $P < 0.001$, Pearson Chi-square (two-tail), Systat). There was no significant difference in object-naming ability.

To distinguish the effects of DBS from those produced by the rehabilitation program or by repeated exposure to the testing procedures, we performed a logistic regression analysis (see Supplementary Information). During the crossover phase, traditional rehabilitation efforts continued, but exposure to DBS alternated on a monthly basis. Thus, behavioural changes that were temporally linked to DBS should be modulated in an approximately square-wave fashion, whereas effects due to rehabilitation or the evaluation process itself are expected to grow gradually over time. The regression model has three parameters (A, B and C), each determining the strength of a potentially contributing influence. The A-term represents the overall probability of obtaining the higher rating on a given scale. (For this analysis, rating scales were dichotomized into two classes of approximately equal size.) The B-term allows this probability to increase or decrease gradually as a function of elapsed time. The C-term allows

this probability to be modulated by the recent stimulation history. The model was applied, in separate analyses, to the three behavioural measures that improved significantly during the crossover phase (CRS-R Arousal, limb control and oral feeding; Fig. 4, Supplementary Fig. 2a,b and Supplementary Table 3). For all analyses, including the *C*-term (reflecting behavioural modulation tracking the stimulation course) in the model leads to a significant improvement ($P < 0.005$ or $P < 0.001$; bootstrap confidence interval on *C*-term significant at $P < 0.01$ for all models). Inclusion of the *B*-term, which reflects gradual change, produces only negligible improvement in the model (not significant for arousal and oral feeding, $P < 0.05$ for limb control but 95% confidence interval for *B*-term includes zero). These analyses indicate that nearly all of the systematic changes in ratings were temporally linked to DBS stimulation, and could not be accounted for by a gradual improvement over time. In addition, logistic regression analyses showed that improvements in intelligible verbalization and limb control were also directly linked to the DBS-on condition during the titration phase (Supplementary Information).

The observed improvements in arousal level, motor control and behavioural persistence might reflect direct activation of frontal cortical and basal ganglia systems that are innervated by neurons within the anterior intralaminar regions and adjacent paralaminar regions of thalamic association nuclei. These neurons act as a key intermediary system and common final pathway for brainstem arousal systems and frontal lobe regions that exert executive control of effort regulation, working memory, selective attention and vigilance[6–11].

Anatomical studies in nonhuman primates have shown that the central lateral nucleus and surrounding paralaminar regions widely innervate the premotor and supplementary motor cortices, providing several monosynaptic pathways that might have been stimulated in our study[20]. We conclude that mesial frontal regions within the supplementary motor area, anterior cingulate cortex and other frontal cortical regions were activated by the electrical stimulation. The frontocentral predominance of cortical activations that were associated with activation of the left DBS lead contacts support this localization, but we cannot exclude the possibility of contributions from surrounding thalamic neurons (see Supplementary Information).

Our focus on patients in a chronic MCS with widely preserved brain structure and clear evidence of interactive behaviour (command following, verbalization and inconsistent communication) is motivated by two important considerations. First, we propose the use of central thalamic DBS to improve the arousal regulation of functionally connected but inconsistently active cerebral networks that might be present in some patients in an MCS but absent in patients in a permanent vegetative state[21]. Second, for patients in an MCS who have not yet recovered reliable communication or functional movements, improvements in response initiation and persistence might restore these abilities.

The behavioural improvements described in this report are notable, given their late emergence and potential functional significance. However, the generalizability of the results is unknown, and expectations raised by this report should be tempered. In particular, our patient followed commands and showed intact language networks in neuroimaging studies[4]. These characteristics will not be shared by all patients in an MCS. Moreover, unknown aspects of this particular subject's brain injury might have influenced his response to DBS. Nonetheless, replication of these findings could have important implications for clinical practice. Although some patients in MCS show clear verbal or gestural 'yes/no' responses, these do not occur consistently enough to be considered reliable. Our patient's recovered ability to interact consistently and meaningfully with others was cited by members of his family as the most important change observed. The restoration of communication also allowed the patient to assume a more active (and interactive) role in his treatment.

These considerations motivate the development of a neuropalliative ethic to establish proportionate goals of care to help

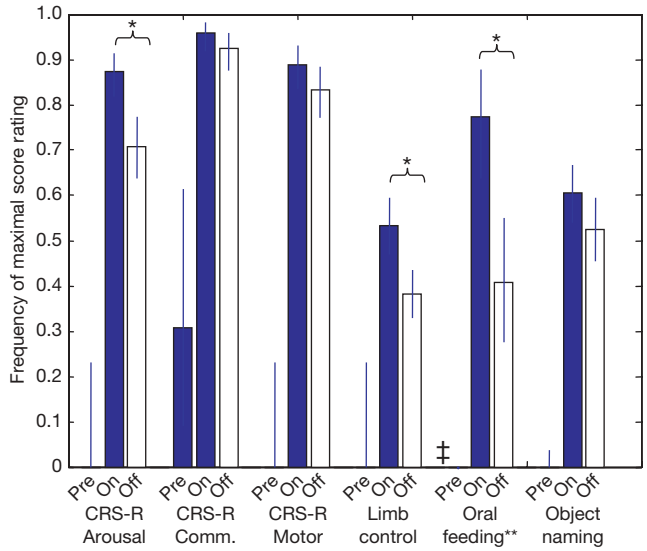

Figure 3 | Comparison of pre-surgical baselines and DBS on and DBS off periods during the crossover phase. Pre-surgical baselines (14 consecutive observations) and crossover phase observations are displayed with 95% confidence intervals for binomial distributions with *n* observations for three CRS-R subscales (Arousal, $n = 185$ off, 189 on; Communication (Comm.), $n = 185$ off, 189 on; Motor, $n = 185$ off, 189 on) and secondary measures (limb movement, $n = 336$ off, 261 on; oral feeding, $n = 54$ off, 53 on; object naming, $n = 206$ off, 235 on). Asterisks indicate significant differences between on versus off for CRS-R Arousal, limb movement and oral feeding ($P < 0.001$ established by Pearson Chi-square (two-tail)). Daggers indicate that oral feeding data were not available before titration; double asterisk indicates that scores 1 and 2 are combined for dichotomy. Pre-surgical baselines for limb control and object naming were converted from CRS-R Motor and CRS-R Oro-motor scores, which remained below the maximal rating across the 14 consecutive observations in the pre-surgical baseline.

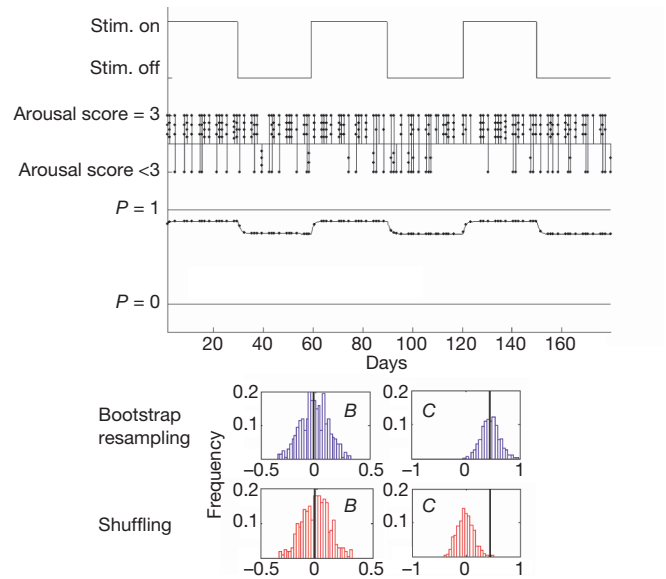

Figure 4 | Logistic regression model of crossover phase arousal data. Figure shows stimulation and behavioural time series, and best-fitting probability model for the behavioural data selected by logistic regression analyses. Single dots on vertical lines within behavioural time series indicate multiple observations on the same day, dots on probability model indicate times of observations. Histograms show bootstrap (blue) and shuffled (red) estimates (500 each) of the coefficients for a linear trend (*B*) and the stimulation history (*C*). Data-derived estimates of the coefficients are shown as black lines. $P = 1$ indicates CRS-R arousal score of 3, $P = 0$ indicates other response categories.

families to balance the potential for improvement against associated burdens while being guided by the patient's previously articulated preferences[22]. Confirmation of these findings in other patients might influence the current practice of excluding individuals with inconsistent behavioural responsiveness from structured rehabilitation programs. Our findings should motivate research to elucidate the mechanisms of recovery and to facilitate the identification of patients who might benefit from neuromodulatory interventions[23].

METHODS SUMMARY

A patient meeting the diagnostic criteria for an MCS proposed by Giacino *et al.*[5] was enrolled as part of a clinical trial of central thalamic DBS. After determination of eligibility, the patient entered into a four-month phase of behavioural evaluation with formal behavioural assessments using the JFK CRS-R[12] to identify subscales that failed to show a ceiling effect. Three subscales (Arousal, Communication and Motor) were prospectively chosen as primary outcome variables in view of the inconsistency in performance on these measures. Subsequently, the patient underwent implantation of bilateral DBS electrodes and post-operative physiological evaluations, including the recording of evoked potentials generated by the stimulation of individual electrode contacts before internalization of electrodes and connection to pulse generators. A DBS titration phase began 50 days after implantation, during which different combinations of frequency, intensity, electrode contact activation and periods of on and off times were tested. At the end of the titration phase, a six-month double-blinded alternating on/off crossover phase began, using optimal parameters that were selected during the titration phase. Secondary outcome measures were developed during the titration phase and included object naming, limb control and oral feeding indices. All primary and secondary outcome measures were tracked prospectively during the crossover phase. During the entire study (from enrolment to completion of the crossover phase), the patient continued to undergo all routine rehabilitation activities. For analysis of DBS data obtained during the on/off crossover phase, we compared binomial data using the Pearson Chi-square (two-tail) test, or the Fisher Exact test when the sample size was insufficient to use the former (Systat). We obtained confidence intervals for binomials using 'binofit' in Matlab 7.0 (Mathworks). Small sample comparisons were completed using the Wilcoxon ranksum test (Matlab 7.0). Logistic regression models of the crossover data were fit using the 'fmincon' routine in Matlab 7.0.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author Contributions N.D.S., J.T.G. and A.R.R. contributed equally to the design, implementation and scholarly preparation of this work. N.D.S. and J.T.G. wrote the manuscript. N.D.S., J.T.G. and A.R.R. acted as principal investigators at their performance sites and participated in all phases of the study including evaluation of data and preparation of all parts of the manuscript. A.R.R. and N.D.S. acted as co-principal investigators for the Investigational Device Exemption (Food and Drug Administration, IDE) covering the use of the brain stimulation methods. N.D.S. acted as principal investigator for the initiation of the project and the development grant that formed the basis of the studies. J.T.G. developed, organized and supervised the collection and primary analysis of behavioural data along with K.K. and an independent statistical consultant (E. Bagiella, Columbia University). J.D.V. assisted with the development of the study design, developed the logistic regression models and supervised this data analysis, and assisted in the preparation of manuscript. K.B. analysed the evoked potential response data and prepared the manuscript presentation of the results; K.B. and N.D.S. collected the evoked potential data. M.G., B.F., B.E. and J.O. collected behavioural data and assisted in the development of secondary outcome measures. C.M. served as the patient's primary care physician and supervised and administered the deep brain electrical stimulation of the patient. Owing to role sequestration, she had no role in data collection or analysis. A.R.R. organized, supervised and carried out the neurosurgical planning, procedures and follow-up, supervised the programming of the neurostimulation and assisted in preparation of the manuscript. J.J.F. developed formal consent procedures and conceptual frameworks with the study primary investigators to address ethical considerations arising in all aspects of the study and preparation of the manuscript. E.J.K., A.M. and K.B. participated in the pre-surgical evaluation, operative and post-operative patient evaluations and neurophysiological evaluations. S.F. provided expert assistance in the design and evaluation of the stimulation protocols. F.P. acted as principal investigator for the planning study for the first year and as a senior advisor throughout the development of the work.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: details accompany the paper on www.nature.com/nature. Correspondence and requests for materials should be addressed to N.D.S. (nds2001@mail.med.cornell.edu).

METHODS

Overview. Pre-surgical assessments were conducted to enable pre-selection of the three primary outcome variables. After completion of the pre-surgical baseline, the patient underwent implantation of bilateral DBS electrodes. The electrodes remained off until initiation of a DBS titration period which began 50 days after implantation, except for a 2-day period of stimulation testing in the immediate post-operative period. Different combinations of frequency, intensity, electrode contact activation and periods of on and off times were tested (see below). At the end of the titration phase, a six-month double-blinded alternating on/off crossover trial began using optimal parameters selected during the titration phase. The Arousal, Motor and Communication subscales of the JFK Coma Recovery Scale — Revised served as the primary outcome measures. The secondary outcome measures were developed during the titration phase and included object naming, limb control and oral feeding indices. All measures were tracked prospectively during the crossover phase.

The subject. A 38-yr-old right-handed man who sustained a closed head injury after an assault 6 yr before the study was enrolled after fulfilling the entry criteria. The patient remained in an MCS according to the criteria proposed in ref. 5. The patient remained medically stable, and structural brain imaging showed no evidence of significant bilateral frontal lesions or injury to the left inferior frontal operculum or the left posterior temporal-parietal region. During the entire study, the patient continued to undergo all routine rehabilitation activities.

Pre-surgical evaluation phase. After selection into the study and determination of eligibility, the patient entered a four-month phase of behavioural evaluation. Towards the end of this phase, formal behavioural assessments using the CRS-R were carried out over a three-week period (twice daily) to identify subscales that failed to show a ceiling effect. Three subscales (Arousal, Communication and Motor) were prospectively chosen as primary outcome variables in view of the patient's inconsistency in performance on these measures.

Electrode implantation and stimulation. After selection for DBS surgery, the patient underwent pre-operative physiological evaluations, implantation of DBS electrodes and post-operative physiological evaluations including recordings from the implanted DBS electrodes before internalization of electrodes and connection to pulse generators.

Post-operative testing phase. Over a two-day period following implantation of the electrode leads, the individual contacts of each electrode were tested to identify voltage thresholds for behavioural effects. During this time, DBS-evoked responses were recorded.

Titration phase. During the titration phase, we obtained CRS-R scores and developed the secondary outcome measures while exploring different stimulation parameters. Observations included comparisons of the frequency of the highest CRS-R subscale scores obtained before surgery with those obtained during titration, and weekly assessments of object naming, functional movements and oral feeding performed by physical, speech, occupational and recreational therapists.

Crossover phase. After the pre-treatment titration phase, we chose a specific parameter set for stimulation for each electrode. The patient then entered into a double-blinded alternating crossover phase of DBS on and off using only these stimulation parameters.

Statistics. All small sample comparisons were completed using the Wilcoxon ranksum test (Matlab 7.0, Mathworks). We compared binomial data using the Pearson Chi-square (two-tail) test, or the Fisher Exact test when the sample size was insufficient to use the former (Systat). We obtained confidence intervals for binomial data using 'binofit' in Matlab 7.0. Logistic regression models were fit using the 'fmincon' routine in Matlab 7.0.

RETRACTION

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Genetic tracing reveals a stereotyped sensory map in the olfactory cortex

Zhihua Zou, Lisa F. Horowitz, Jean-Pierre Montmayeur, Scott Snapper & Linda B. Buck

Nature 414, 173–179 (2001)

This Article described patterns of labelling observed in olfactory cortex when a transneuronal tracer was co-expressed with single odorant receptor genes in the mouse olfactory epithelium. During efforts to replicate and extend this work, we have been unable to reproduce the reported findings. Moreover, we have found inconsistencies between some of the figures and data published in the paper and the original data. We have therefore lost confidence in the reported conclusions. We regret any adverse consequences that may have resulted from the paper's publication.

Author Contributions L.B.B. and L.F.H. conceived the project, L.F.H. and J.-P.M. prepared gene-targeting constructs to generate the mice, S.S. trained Z.Z. in gene-targeting techniques, Z.Z. prepared and analysed the mice and provided all figures and data for the paper, and L.B.B. and Z.Z. wrote the paper. Correspondence and requests for materials should be addressed to L.B.B. (lbuck@fhcrc.org).

CORRIGENDUM

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Behavioural improvements with thalamic stimulation after severe traumatic brain injury

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In this Letter, Tracey Biondi was omitted from the author list. In addition, a sentence in the Author Contributions statement should be revised to read: 'M.G., B.F., B.E., T.B. and J.O. collected behavioural data and assisted in the development of secondary outcome measures.'.

Arousal by stimulation of deep-brain nuclei

Arising from: N. D. Schiff *et al.* *Nature* 448, 600–603 (2007)

Schiff *et al.*[1] show that deep-brain stimulation of the unspecific thalamocortical system through certain midline thalamic nuclei produces an alerting effect in a patient in a minimally conscious state. Such nuclei include the central lateral nucleus, paralaminar regions of the median dorsalis, and the posterior–medial aspect of the centromedian/parafascicularis nucleus complex.

Hassler and colleagues published a similar study, with certain methodological differences, in 1969[2,3]. Their aim was similar, namely the alerting of consciousness by activation of anatomically undamaged neurons in the unspecific thalamocortical system. McLardy *et al.*[4] were also motivated by the same concept, but gave little detail of methodology and failed to produce a result. Several reports followed, but that by Schiff *et al.*, though it concerns only a single case, is the most detailed and is strengthened by its internal statistical control.

Hassler's subject[2] is described as having a post-traumatic apallic state. This term derives from the original description by Kretschmer[5] of a state of waking either without awareness (as seen in the vegetative state), or with minimal awareness (as in the minimally conscious state). Hassler stimulated pallidum on the basis that it feeds into the unspecific system as well as the specific system. This view was supported at the time by the elicitation of recruiting responses (incremental high-voltage synchronizing waves, usually, though not always, of long latency, carried over the unspecific thalamocortical system[6]) by stimulation of pallidum[7]. The dipole for such laminar field potentials is in the superficial layers of the cortex[8]. This is perhaps concordant with the later demonstration of the ubiquitously distributed matrix of calbindin-immunoreactive neurons, which project to the superficial layers of wide areas of cortex[9,10]. Hassler also chose the basal portion of, using his terminology, the latero–polar nucleus of the thalamus on the opposite side.

As a neurologist, a neuroanatomist who wrote the anatomy of the thalamus for the Schaltenbrand stereotactic atlas, and someone with a wide experience of stereotaxy, Hassler was well placed to make the foregoing contribution.

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Schiff et al. *reply*

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Staunton[1] highlights prior work applying deep-brain stimulation (DBS) in related thalamic and other subcortical structures in vegetative-state patients. We focused on patients who have plateaued at the upper end of the minimally conscious state at least one year after injury[2], a group distinct from patients remaining in or just above vegetative state within the low end of the minimally conscious state. Patients remaining in a chronic vegetative state have anatomic pathology consistent with widespread neuronal death and cerebral disconnection[3]. In these patients, forebrain structures within the corticostriatopallidal–thalamocortical systems have been overwhelmingly damaged .

The paper by Hassler *et al.*[4] cited by Staunton is one of several early studies that culminated in a large multicentre series of vegetative-state patients implanted with DBS systems in the centromedian thalamus[5,6]. Those studies found that acute arousal responses occurred in the majority of patients, who nonetheless did not improve. Arousal responses *per se*, including wide eye-opening, changes in autonomic function and shifts to higher-frequency content ('desychronization') of the electroencephalogram reflect a basic and broad activation of forebrain, brainstem and spinal cord systems[7]. Notably, these earlier studies demonstrated that acute arousal responses alone are not predictive of an effect on outcome, nor do they imply a role for DBS in the sustained recovery of higher integrative brain function.

The prior literature must be examined for two distinct aspects of study design. The first is that in earlier studies of DBS in vegetative-state patients, the patient-selection criteria did not ensure that patients were unlikely to recover function spontaneously. The few patients with traumatic brain injuries labelled as 'responders' were studied 3 to 6 months into their recovery course[5]. The probability of recovery of consciousness for these patients (and the Hassler patient[4]) ranged from 35% to 16%[8,9]. Moreover, these few patients have since been reclassified by the investigators as having been in minimally conscious state[10]. Smaller prospective studies of such patients indicate that the likelihood of recovery of consciousness by one year from minimally conscious state at 3–6 months after traumatic injury is significantly higher[11,12].

The second design issue is that evaluation of the effects of DBS were not carried out in a formal, blinded fashion to allow assessment of the effects on behaviour, even within a single patient. To assess a causal influence of DBS on recovery, formal neurobehavioural assessments are essential to establish baseline diagnosis, assure that natural recovery has plateaued, and to track emergence of cognitively

mediated behaviours induced by DBS. That further recovery was incidental to the application of DBS in these earlier studies has remained statistically likely. In contrast, our patient had been formally assessed, with stable behavioural profiles for more than 6 years, making spontaneous recovery from minimally conscious state very unlikely; also, DBS effects were tracked and shown to be causal to behavioural recovery[2].

Although other thalamic and subcortical structures produce arousal responses when stimulated, we chose our targets because of their specific anatomical and physiological properties, not shared by the globus pallidus or centromedian nucleus (which does not have strong projections to the cortex). The central lateral nucleus and surrounding regions have reciprocal monosynaptic connections with the medial frontal regions supporting arousal regulation, receive very dense innervation from brainstem arousal systems, and have diffuse inputs to the striatum, among other unique specializations supporting the use of this target[13].

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