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CHAPTER 10

Waking up the brain: a case study of stimulation-induced wakeful unawareness during anaesthesia

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Abstract: Hitherto, little is known about the specific functional contributions of extrathalamic arousal systems to the regulation of wakefulness in humans. Here, we describe a 42-year-old woman with treatment resistant tremulous cervical dystonia who underwent microelectrode-guided stereotactic implantation of deep brain stimulation (DBS) electrodes in the internal segment of the globus pallidus internus (GPi) under general anaesthesia. Acute unilateral DBS of circumscribed sites within the subpallidal fibre-field with 130 Hz caused a transient state of wakefulness with an increased responsiveness to external stimuli but without detectable signs of conscious awareness. The extent of behavioural arousal could be titrated as a function of stimulus intensity. At lower stimulation intensities, bilateral eye opening occurred in response to verbal commands or tactile stimulation. At suprathreshold intensities, the patient's eyes remained open and conjugated throughout the stimulation period. The arousal effect ceased abruptly when DBS was discontinued. Behavioural arousal was accompanied by global cortical EEG activation in the gamma-frequency range (40–120 Hz) and by autonomic activation as evidenced by increased heart rate. The observed effect was reproducible in both hemispheres and topographically restricted to 6 out of 15 tested sites in the fibre-field between the GPi and the posterior aspect of the basal nucleus of Meynert. We conclude that the stimulated neural substrate in the subpallidal basal forebrain is involved in the premotor control of lid and eye position and the control of the activation state of the human neocortex. It may thus be important for the induction and maintenance of anaesthesia-induced unconsciousness in humans. It is suggested that subpallidal DBS released a downstream arousal circuit from anaesthesia-related inhibitory modulation either by direct excitation of an arousal nucleus or by inhibition of a sleep-promoting centre in the basal forebrain.

Keywords: arousal; general anaesthesia; deep brain stimulation; nucleus basalis of Meynert; dystonia

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Introduction

Both sleep and anaesthesia are reversible states of eyes-closed unresponsiveness to environmental stimuli in which the individual lacks both wakefulness and awareness. In contrast to sleep, where sufficient stimulation will return the individual to wakefulness, even the most vigorous exogenous stimulation cannot produce awakening in a generally anaesthetized patient. In clinical practice as well as everyday life, awakening from sleep or anaesthesia is commonly defined as opening of the eyes in response to verbal commands (Dutton et al., 1995). The palpebral fissures widen, the eyes are fixed in the primary position, the striated muscle tone is enhanced throughout the body and large cardio-respiratory changes occur (Horner et al., 1997). These physiological concomitants of wakefulness are brought into action more or less simultaneously by a global state change within the central nervous system (Pfaff et al., 2008). In the mammalian neocortex, this state change is reflected in a characteristic transformation of the spectral content of electroencephalographic recordings (EEG) known as 'activation' or 'desynchronization': During the transition from sleep or anaesthesia to waking, low-frequency activity with high amplitudes (the EEG signature of sleep and anaesthesia) is replaced by low amplitude EEG fluctuations at relatively high frequencies (>15 Hz), which are indicative of the awake and aroused state (Steriade et al., 2001).

Moruzzi and Magoun (1949) demonstrated that electrical stimulation of brainstem-thalamic projections switches the neocortex of anaesthetized animals into an arousal state. Their pioneering work laid the foundations for our current understanding of the midbrain reticular formation and midline thalamic structures as important nodal points of an ascending neural network which exerts a tight control over the activation state of the cortex and the level of wakefulness (Steriade, 1996). Later work with implanted electrodes in unrestrained animals showed that behavioural arousal is accompanied by similar EEG changes irrespective of whether alerting occurs naturally or is mimicked by electrical stimulation (Steriade and McCarley, 2005). Some of the classical electrocortical and behavioural arousal responses seen in laboratory animals have been replicated during electrical test stimulation in humans undergoing stereotactic surgery in the thalamus for different pathological conditions, including movement disorders (Hassler et al., 1960; Housepian and Purpura, 1963), neuropsychiatric disorders (Velasco et al., 2006) or epilepsy (Velasco et al., 1997). Although only rarely observed (Schaltenbrand et al., 1973; Umbach, 1961), these artificial conditions mimicking natural arousal raised the particular interest of clinicians and resulted in clinical applications of thalamic deep brain stimulation (DBS) for otherwise untreatable patients with serious abnormalities of arousal or behavioural responsiveness resulting from severe brain injury (Hassler et al., 1969; Katayama et al., 1991; Schiff and Plum, 2000; Yamamoto et al., 2002). Progressive arousal and improved neurological function following thalamic DBS has recently been demonstrated in a minimally conscious patient (Schiff et al., 2007), further highlighting the outstanding role of the midline thalamus as an arousal-regulating relay and appropriate site for neuromodulatory interventions in disorders of consciousness. Moreover, the midline thalamus also plays an important role in the regulation of anaesthetic-induced unconsciousness (Alkire et al., 2000; Fiset et al., 1999; Franks, 2008; Keifer, 2003; Stienen et al., 2008).

The anatomy of subcortical arousal systems producing wakefulness is, however, more complex than initially thought. The view has emerged that, rather than operated by a single transthalamic arousal system, arousal-control is regulated by an orchestration of different subcortical arousal- and sleep-promoting systems that act in parallel and involve different neurotransmitters (Franks, 2008; Jones, 2008). The dynamics of thalamo-cortical activity depends not only on ascending influences from the mesencephalon (Francesconi et al., 1988; Munk et al., 1996), but is also modulated by inputs from the hypothalamus and basal forebrain (Buzsaki and Gage, 1989; Franks, 2008; Pinault and Deschenes, 1992; Semba, 1991; Steriade and Buzsaki, 1990; Steriade and McCarley, 2005). Several lines of evidence stress the importance of arousal-related neuronal populations located in

the basal forebrain area extending between the globus pallidus internus (GPi) and the nucleus basalis Meynert (NBM) in the regulation of cortical arousal and wakefulness (Buzsaki and Gage, 1989; Semba, 1991). First, recent electrophysiological studies have revealed strong correlations between the firing of individual cholinergic and GABAergic basal forebrain cells and cortical activity across the sleep–wake cycle (Lee et al., 2004, 2005; Lin et al., 2006). Both the cholinergic and the non-cholinergic components are thought to play a key role in switching the neocortex into an arousal state characterized by high-frequency EEG activity, particularly in the gamma band (30–80 Hz) (Detari, 2000; Detari et al., 1999; Jones, 2008; Lee et al., 2005; Lin et al., 2006). Second, in agreement with the state-dependence of basal forebrain neurons across sleep stages demonstrated in rodents, basal forebrain structures in humans exhibit significant changes in glucose metabolism or blood flow throughout the sleep–wake cycle (Braun et al., 1997; Nofzinger et al., 1997; Zaborszky et al., 2008). Third, experimental lesions of the NBM induce deficits in performance on a wide variety of tasks requiring selected attentional abilities (Dunnett et al., 1991; Wenk, 1997) and result in a slowing of EEG activity (Buzsaki et al., 1988; Buzsaki and Gage, 1989). Finally, electrical stimulation of these arousal populations has demonstrated a role in both EEG desynchronization (Belardetti et al., 1977; McLin et al., 2002; Metherate et al., 1992) and behavioural arousal (Grahnstedt and Ursin, 1980). Low awakening thresholds in sleeping animals and effective stimulation sites that elicit cortical activation have repeatedly been observed in the middle and ventral aspects of the GPi and subjacent NBM (Grahnstedt and Ursin, 1980; Metherate et al., 1992).

Hitherto, the contribution of basal forebrain populations to arousal has not been directly tested in humans, mainly due to the difficulty to assess these small subcortical structures (Baars, 1995). However, the nearby ventral posterolateral aspect of the GPi is commonly targeted in surgery for movement disorders (Vitek et al., 1998). Microelectrode recording and stimulation techniques that are regularly employed during pallidal interventions, may thus also provide important insights into functional contributions of the GPi/NBM area in a large-scale arousal-regulatory network between brainstem and cortex.

The present case report demonstrates and discusses the phenomenon of transient awakening from general anaesthesia induced by unilateral intraoperative DBS in the GPi/NBM area. The aim of the present study was twofold: (i) Our first goal was to determine the anatomical substrates involved in the arousal effect. To this end, we precisely delineated the stimulation sites using intraoperative microelectrode mapping and performed a stereotactic analysis for electrode localization on fused computerized tomography/magnetic resonance imaging (CT/MRI) data. (ii) The second goal was to study the behavioural and electrophysiological accompaniments of this arousal modulation. Therefore, we employed EEG and electrocardiographic (ECG) recordings as central and peripheral arousal indices, respectively. Some of the results of this study have been presented in abstract form (Moll et al., 2007).

Material and methods

Patient details

A 42-year-old female with a 27-year history of involuntary turning and twisting of the neck was presented for surgical evaluation. At the onset, she developed an abnormal head posture in conjunction with intermittently occurring tremulous head movements triggered by stress. Symptoms were present during and interfered with most daily activities, such as reading, walking or car driving. No other body parts were affected. Head tremor was alcohol sensitive for a few years, but maximum pharmacological treatment with various anti-tremor drugs (including benzodiazepines, anticholinergics, beta-blocker and L-Dopa) was largely ineffective. She also underwent psychotherapy which was unsuccessful. Other family members were not affected by movement disorders. The head tremor became increasingly severe and socially embarrassing during the last 3 years. Due to the disease progression, the patient

had to give up her position as a hotel receptionist and subsequently developed reactive depression. She was referred to our hospital in 2005 for further assessment and local botulinum toxin injections. On examination, the patient had a constant, irregular, slow (3-Hz) head tremor (primarily horizontal 'no-no' movements) at rest along with a 15° rotation of the head to the right and a slight tilt to the left. There was an elevation and forward displacement of the left shoulder. Head tremor was rated as severe (Score 4, amplitude > 2 cm) using the Fahn–Tolosa–Marín Tremor Rating Scale (range 0–4) (Fahn et al., 1988). Severity of cervical dystonia was scored 11 on the severity subscale of the Toronto Western Spasmodic Torticollis Rating Scale (range 0–35) (Consky and Lang, 1994). The patient was capable to suppress abnormal head movements by supporting the chin with both hands or by adopting an abnormal head position and posture. Apart from abnormal head movements and postures, neurological examination was unremarkable. Repeated administration of botulinum toxin was associated with side effects. She was therefore considered a suitable candidate for implantation of DBS electrodes. The patient provided written informed consent before the surgical intervention in February 2006. All procedures were approved by a local ethics committee and conducted in accordance with the declaration of Helsinki. Due to the severity of the head tremor, the stereotactic operation was performed under general anaesthesia.

Anaesthetic procedure

As a premedication before surgery, the patient received 7.5 mg midazolam. Venous and arterial cannulae were inserted for fluid and drug administration and monitoring of arterial blood pressure. General anaesthesia was induced with a bolus of 2 mg/kg propofol and maintained by application of 6 mg/kg/h propofol in combination with 0.25 μg/kg/min remifentanil. The patient was mechanically ventilated via an endotracheal tube with an oxygen–air mixture (FiO_2 0.5). Anaesthetic depth was constantly monitored throughout the operative course at regular intervals by an experienced anaesthesiologist and adequacy was deduced from clinical signs such as complete unresponsiveness, lack of spontaneous movements, stable heart rate (HR) and blood pressure. With the exception of stimulation-induced changes (see below), the patient did not respond to verbal commands, prodding or any other sensory stimuli, no spontaneous movements occurred and autonomic measures remained stable throughout the whole surgical procedure. The level of anaesthesia continued to be on a constant level after the test stimulation (including skin incision and trepanation of the skull on the second hemisphere), so that no adjustment of the anaesthetic drugs was necessary for the subsequent steps of the procedure.

Stereotactic intervention

Because the patient had tremulous cervical dystonia (and no 'pure' head tremor) the posteroventrolateral GPi instead of the ventrolateral thalamus was targeted. Details of the surgical procedure are reported elsewhere (Hamel et al., 2003). Briefly, a MRI-compatible Zamorano–Dujovny frame (Stryker Leibinger, Freiburg, Germany) was mounted on the patient's head and tightly secured with pins. Both gadolinium-enhanced volumetric T1 MRI and T2 weighted spin echo MRI sequences were acquired (1.5 Tesla Magnetom Sonata, Siemens, Erlangen, Germany) and fused with a CT scan (Somatom Plus 4, Siemens, Erlangen, Germany) using commercially available software (iPlan, BrainLAB Inc., Westchester, IL, USA). Except for a small non-specific lesion in the right subcortical white matter of the parietal operculum, the brain appeared regular and inconspicuous on acquired anatomical MRI scans. After determining a reference-line connecting the anterior and posterior commissure (AC-PC line, length 23.6 mm; width of the third ventricle < 3 mm), the GPi was targeted 20 mm lateral to the AC-PC line, 3 mm inferior and 3 mm anterior to the mid-commissural point on both sides. The approach angles for the left and right side, respectively were 32/23 degrees from the AC-PC line in the sagittal projection (rostral inclination), and 15/13

degrees from the vertical in the coronal projection. A burr hole was made anterior to the left and right coronal suture, the micromanipulator was mounted on the stereotactic frame and the appropriate target coordinates were adjusted.

Microelectrode recordings

Microelectrode recordings were performed with five parallel tracks arranged in a concentric array (MicroGuide, Alpha-Omega, Nazareth, Israel). Four outer platinum–iridium electrodes (impedances, 0.3–0.8 MegaOhm at 1000 Hz; FHC Inc., Bowdoinham, ME, USA) were separated by 2 mm from a central one which aimed at the theoretical target. Signals were amplified ($\times$ 20.000), bandpass-filtered (300–6000 Hz) and digitized (sampling rate: 24 kHz). Spike detection was performed offline using a voltage threshold method and single units were then separated by manual cluster selection in 3D feature space using principal component projections of the waveforms (Offline-Sorter, Plexon Inc., Dallas, TX, USA). Spiketrain-analysis was applied to well-isolated single cell activity sampled for at least 30 s or 1000 action potentials (Neuroexplorer, Nex Technologies, Littleton, MA, USA).

Test stimulation

Following microelectrode-guided delineation of pallidal boundaries and identification of the optic tract, we aimed to assess the relative proximity to the internal capsule by determining the thresholds of stimulation-induced muscle contractions (as evidenced by apparent limb movements and/or the appearance of EMG-activity) or eye deviations. To this end, monopolar test stimulation was performed at different depth levels (see below) using the uninsulated macrotip of the electrode (cathodal) against the respective guide tube (anodal). The stimulus intensity was graduated in volts. With a macrotip impedance of $\sim$1 kOhm, 1 V would generate a current of $\sim$1 mA. In each stimulation site, the amplitude was gradually increased in steps of 0.5 V up to 7 V over a period of approximately 2–3 min, always at a frequency of 130 Hz (impulse width, 60 μs). To assess the distance to motor fibres in the adjacent internal capsule, we also carried out low-frequency stimulation in the posterior and medial stimulation sites on each hemisphere (frequency, 4 Hz; impulse width, 100 μs). The interval between individual electrical stimulation periods varied, but always exceeded 30 s.

Electrophysiological monitoring and analysis

In parallel with the microrecording signals, a 32-channel system (AlphaMap, Alpha-Omega, Nazareth, Israel) was used to amplify and record EEG (amplification $\times$ 5.000; bandpass, 1–300 Hz), EMG (amplification $\times$ 2.000; bandpass, 5–1000 Hz) and ECG signals at a sampling rate of 3.000 Hz during the microrecording and stimulation periods. EEG was recorded from four scalp electrodes (Ag/AgCl cup electrodes filled with conductive gel; Nicolet Biomedical, Madison, WI, USA) approximately placed at Pz, Oz, C3 and C4 according to the international 10–20 system against the left earlobe as a common reference. Spectral power was calculated in 5 s windows with a 2.5 s overlap with a 0.5 s block size/frequency resolution of 2 Hz (Matlab, Mathworks Inc., Natick, MA, USA). All windows were normalized to the mean power in each frequency bin in the rest period (16 windows) between the two stimulation periods. The grey scale (Fig. 4A) therefore reflects the difference between this interim period and the stimulation periods, which can be clearly identified by the stimulation artefact at 130 Hz. To quantify and compare the spectral changes following stimulation at different brain sites, spectral power was calculated for a 65 s segment of EEG recorded from the occipital midline electrode (Oz) during stimulation with each of the five macrotips in the secondly operated right hemisphere. In each case, the data was taken from the end of the stimulation period where the stimulus magnitude was largest. Spectra were calculated with a 1 s block size/frequency resolution of 1 Hz. Each power spectrum was normalized to baseline, using power values calculated for a rest period (no stimulation) of the same length recorded between the stimulation epochs. The concurrent recording from a three-lead ECG and

multiple surface electrodes placed above selected muscles on both sides of the body (including sternocleidomastoid, biceps brachii, triceps brachii, deltoid, flexor digitorum superficialis, extensor digitorum communis, quadriceps, gastrocnemius and tibialis anterior muscle) allowed the assessment of stimulation-induced effects on the HR and muscle-activity, respectively. All results are given as the mean $\pm$ S.D.

Results

Microelectrode-guided delineation of the stimulation sites

Microelectrode recordings started 15 mm above the theoretical target and allowed a precise delineation of the external and internal pallidal segments. Sporadic putaminal activity was encountered close to the dorsal boundary of the GPe (Fig. 1A), confirming a lateral plane of at least 20 mm to midline (Vitek et al., 1998). The mapping of the internal medullary lamina allowed a further division of the GPi into its external and internal divisions GPie and GPii, respectively. Neurons from the GPii fired somewhat faster (18.8 ± 17.2 Hz, $n = 18$) than neurons of the GPie (13.7 ± 7.1 Hz, $n = 25$) and GPe (11.5 ± 9.2 Hz, $n = 24$), however, this difference was not significant (Student's t-test, $p > 0.1$). Figure 1A,B show representative striatal and pallidal recordings, respectively. The pallidal base was recognized by sparseness of neuronal activity, as the electrodes were moved to the adjacent subpallidal fibre-field. Figure 1C provides a depth profile with a synopsis of all recording sites from both hemispheres. To assess the distance to the neighbouring optic tract, changes in background neuronal activity were examined during brief light stimuli applied with a torch in darkened conditions. At a depth level of 5 mm below AC-PC (2 mm below the pallidal base), the central and anterior electrodes on the left side showed increases and decreases of background neuronal activity, which followed the onset and offset of the transient light stimuli, respectively. In the right hemisphere, only the medial electrode displayed optic tract activity 6 mm below AC-PC. Following offline rectification, these responses could readily be visualized (Fig. 2A). The lack of recordings from both posterior trajectories indicated that these tracks traversed mainly fibre tracts of the adjacent internal capsule, being further substantiated by the identification of the microexcitable internal capsule in these positions (Fig. 2B, see below).

Behavioural arousal

Following characterization of light responses, test stimulation was carried out on each of the five microelectrodes at two different depth levels on the left (2 and 4 mm below AC-PC) and one depth level on the right side (4 mm below AC-PC), adding up to a total of 15 tested sites. We observed that stimulation in 6 out of 15 tested sites led to reproducible behavioural expressions of wakefulness without detectable signs of conscious awareness. Stimulation elicited enduring bilateral opening of the eyelids with the eyes in a near conjugate position (Fig. 3B), whereas in the absence of stimulation the patient's eyes were closed (Fig. 3A) and presented a divergent strabismus. When stimulation was carried out with intensities below the threshold for persistent eye opening, phasic behavioural arousal with transient eye opening in response to auditory or tactile stimuli could also be induced. The patient stereotypically opened the eyes with a short delay (700–1000 ms) in response to addressing the patient verbally or to pinching the patient's arms — indicating a stimulation-induced increased responsiveness to external stimuli. At all sites tested, the behavioural arousal persisted only during the course of stimulation and disappeared promptly with termination of stimulation, following which the patient could not be roused anymore by loud commands or any other stimuli. On the first operated left side, an arousal effect could be elicited by stimulation at two different sites: posterior electrode, 4 mm below AC-PC (threshold: 3.0 V) and anterior electrode, 2 mm below AC-PC (threshold: 2.0 V). On the right hemisphere, the arousal effect was elicited only with higher stimulus intensities at four different sites (depth level 4 mm below AC-PC): central (threshold: 5.0 V), medial (threshold:

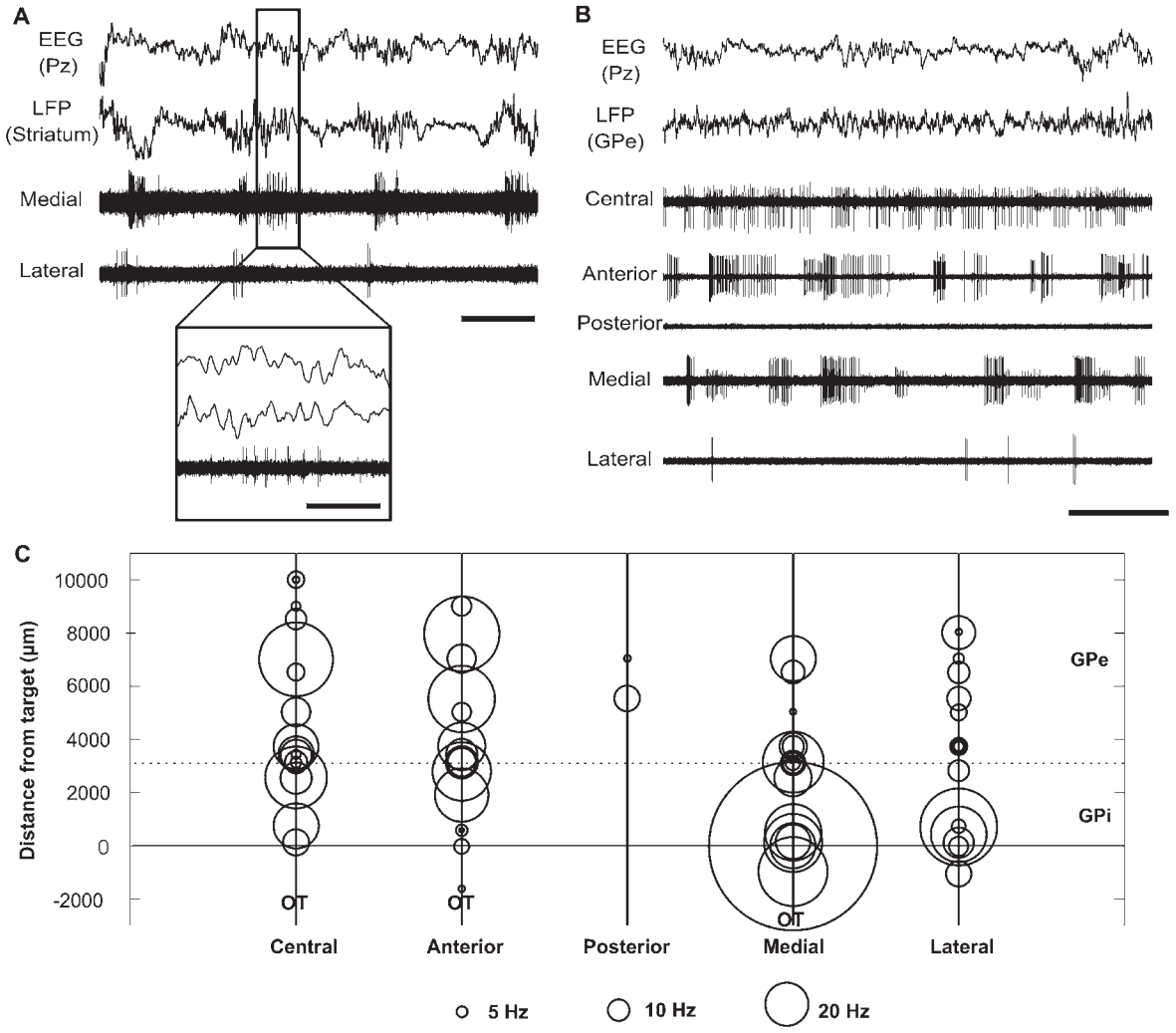

Fig. 1. Results of intraoperative microelectrode mapping. (A) Recording from the striatum, 12.7 mm above target. Note the burst-suppression pattern in the EEG and striatal LFP with alternating episodes of spindling activity and low-amplitude signals. Scale bar, 2 s. The two recorded striatal units fire at spindle onset and are completely silent during low-amplitude periods of EEG/LFP activity. Inset shows spindling-related activity of the striatal unit recorded from the medial track in the alpha-frequency range (10–12 Hz). Scale bar, 500 ms. (B) Representative example of microelectrode recordings from the GP of the left hemisphere (2.3 mm above the pallidal base). Central, anterior and medial tracks exhibit an irregular, uncorrelated bursting pattern. The lateral electrode picks up striatal cellular activity, while the posterior track traverses fibres of the internal capsule. Scale bar, 2 s. (C) Synopsis of mapping results (data from both hemispheres pooled). Activity-depth profiles are given for each microelectrode track, with circles representing the location and mean firing rate (circle size) of the recorded cell. The virtual absence of cellular activity in the posterior tracks suggests a course traversing the internal capsule. OT, optic tract.

5.7 V), posterior (threshold 4.5 V) and lateral (threshold: 7 V). Low-frequency stimulation (frequency 4 Hz, impulse width, 100 µs) did not lead to behavioural, cortical or autonomic activation at any of the tested sites (not shown).

Cortical activation

The described stimulation-induced behavioural arousal was associated with global low-voltage high-frequency activity in the EEG. The EEG

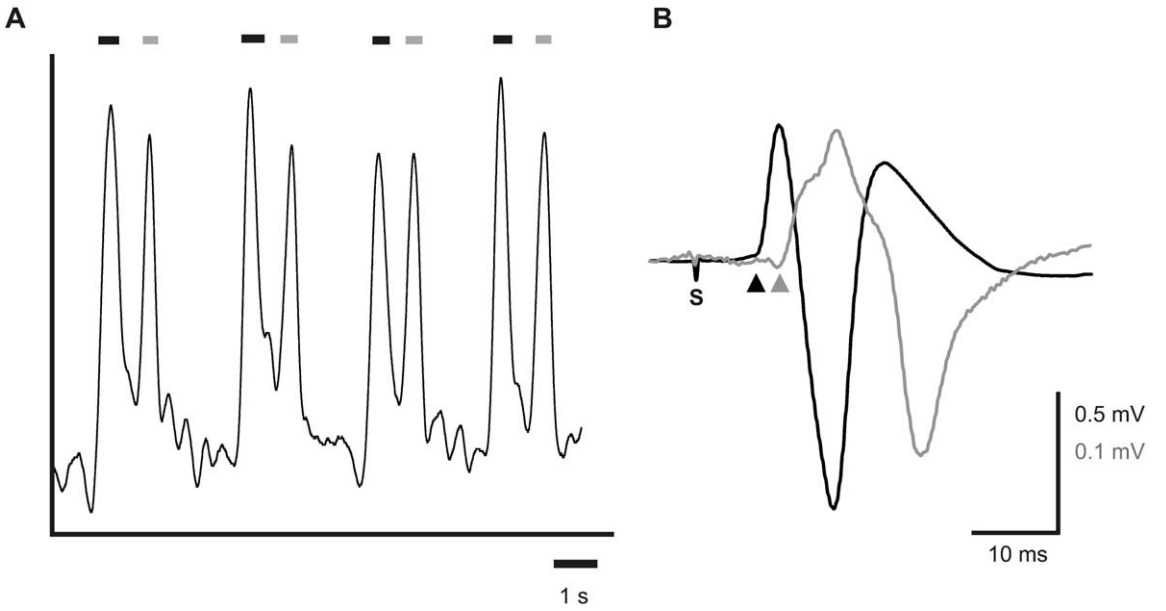

Fig. 2. Physiological identification of anatomical landmarks. (A) Optic tract response at a depth level of 5 mm below AC-PC; left hemisphere, medial electrode. The graph displays the time course of multi-unit activity after offline rectification and smoothing. Note the increases and decreases of background neuronal activity associated with transient light stimuli. Black and grey bars indicate movements of the torch onto and away from the pupil, respectively. (B) Motor-evoked potentials in the left m. sternocleidomastoideus (black) and m. biceps brachii (grey) following electrical stimulation of motor fibres in the right internal capsule, 2 mm below AC-PC plane, with low frequency. Latencies are 7 ms for the sternocleidomastoid (black arrowhead) and 9.5 ms for the biceps muscle (grey arrowhead), respectively. S, stimulus artefact. Note the difference of the two graphs in amplitude scaling.

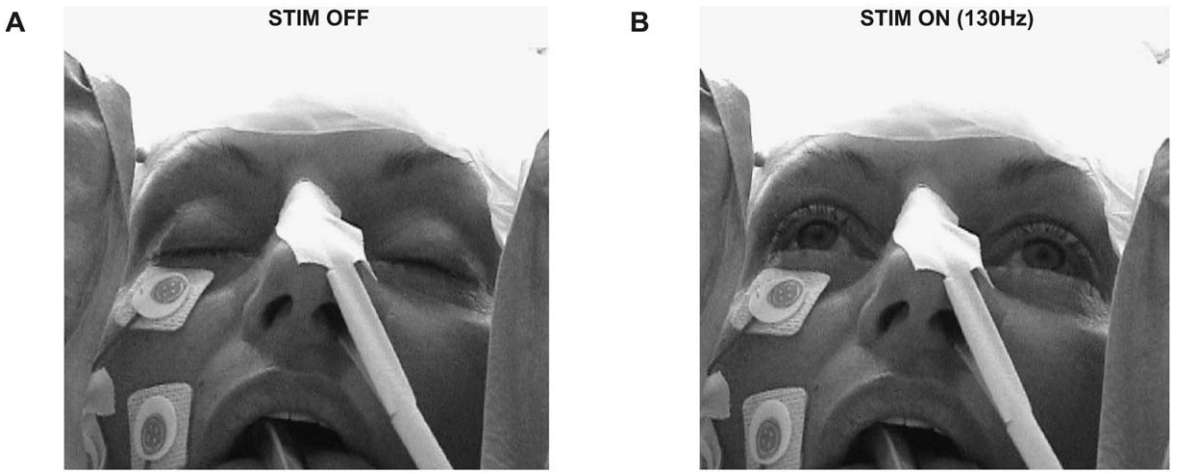

Fig. 3. Behavioural arousal. Photographs of the stimulation-induced behavioural effect. (A) Patient without stimulation. (B) Arousal reaction consisting of sustained eye opening during suprathreshold electrical stimulation of the left anterior electrode with 130 Hz at 2 V. Note the near conjugate position of the eyes. Patient consent has been obtained to publish this figure.

desynchronization showed a bilateral scalp distribution. Power spectral analysis showed that 130 Hz DBS was correlated with increased power at beta (>20 Hz) and gamma-frequencies (>40 Hz), the augmentation of which was in close correspondence with behavioural arousal. Figure 4A,B show spectrograms computed for a continuous EEG recording from an electrode placed above the left sensorimotor cortex (corresponding approximately to position C3 in the standard 10–20 system) during high-frequency stimulation of the medial and posterior electrodes in the first operated left hemisphere, respectively. Stimulation of the medial test-electrode (the first stimulation period), which did not lead to behavioural arousal, produced little change in the power at any frequency. Subsequent stimulation of the posterior test-electrode, which caused behavioural arousal with sustained eye opening at a threshold of approximately 3 V, led to an increase in power in the higher gamma-frequency range (>60 Hz), the magnitude of which increased with the intensity of stimulation. The fact that this increase was not seen during identical stimulation using the medial electrode, around 1.5 mm away, makes it highly unlikely that the change in spectral content of the EEG was an artefact of the electrical stimulation. Stimulation-induced power changes were observed to be especially pronounced in the delta (1–4 Hz) and higher gamma-frequency range (60–95 Hz). Minor power changes occurred in other frequency bands (theta, alpha and beta, not shown). Figure 5 shows a comparison between stimulation-induced power changes of the occipital midline EEG (Oz) in the delta band (1–4 Hz; left panel) and the higher gamma band (60–95 Hz; right panel) during stimulation of the five different trajectories on the second (right) hemisphere. Gamma-band power increases were greater at depth stimulation sites that also produced behavioural arousal. Changes in the gamma band were generally larger in magnitude than those in the delta band. A decrease in delta-power was observed in the two instances, where DBS led to both behavioural and autonomic activation (posterior and lateral trajectory).

Autonomic and electromyographic activation

In 6 of the 15 tested positions, electrical stimulation led to a significant autonomic activation, as revealed by a transient HR increase of 9 ± 2 beats min^{-1} (bpm) compared to the baseline HR (Student's paired *t*-test, $p = 0.01$, $n = 6$). In four of these six sites, stimulation produced autonomic activation without behavioural or EEG arousal, respectively. As Fig. 4B illustrates, the HR increase was particularly pronounced, when stimulation was associated with behavioural and EEG arousal (increase of 15.5 ± 3.5 bpm; 2/6 stimulation sites): Stimulation of the medial trajectory (Fig. 4B; first stimulation period, left section) on the first operated left hemisphere and 3 mm below AC-PC failed to induce a clinical and electrophysiological arousal response and did not increase the patient's HR. However, an EMG response of the contralateral biceps muscle was obtained upon electrical stimulation in this position, confirming the proximity of the medial trajectory to motor fibres running in the posterior limb of the internal capsule. In contrast, during stimulation of the posterior trajectory (Fig. 4B; second stimulation period, right section) with similar parameters (pulse-width, 60 μs; frequency, 130 Hz; amplitude stepwise increased from 0.5 to 5 V), the EMG remained silent. In this position, stimulation evoked behavioural as well as EEG arousal and was accompanied by a transient increase of the patient's pulse from 55 to 70 bpm. The arousal effect ceased abruptly after stimulation was discontinued and HR returned to baseline values. On the second operated right hemisphere, the topographic relationship of medial and posterior stimulation sites to the microexcitable internal capsule was different. High-frequency stimulation of the medial trajectory (4 mm below the AC-PC plane) did not lead to EMG changes, whereas stimulation of the posterior trajectory induced tetanic contractions of different contralateral arm (m. extensor digitorum communis, threshold: 5.0 V; m. biceps brachii, threshold: 5.5 V) and neck muscles (contralateral sternocleidomastoid muscle, threshold: 5.5 V). Using low-frequency stimulation in this

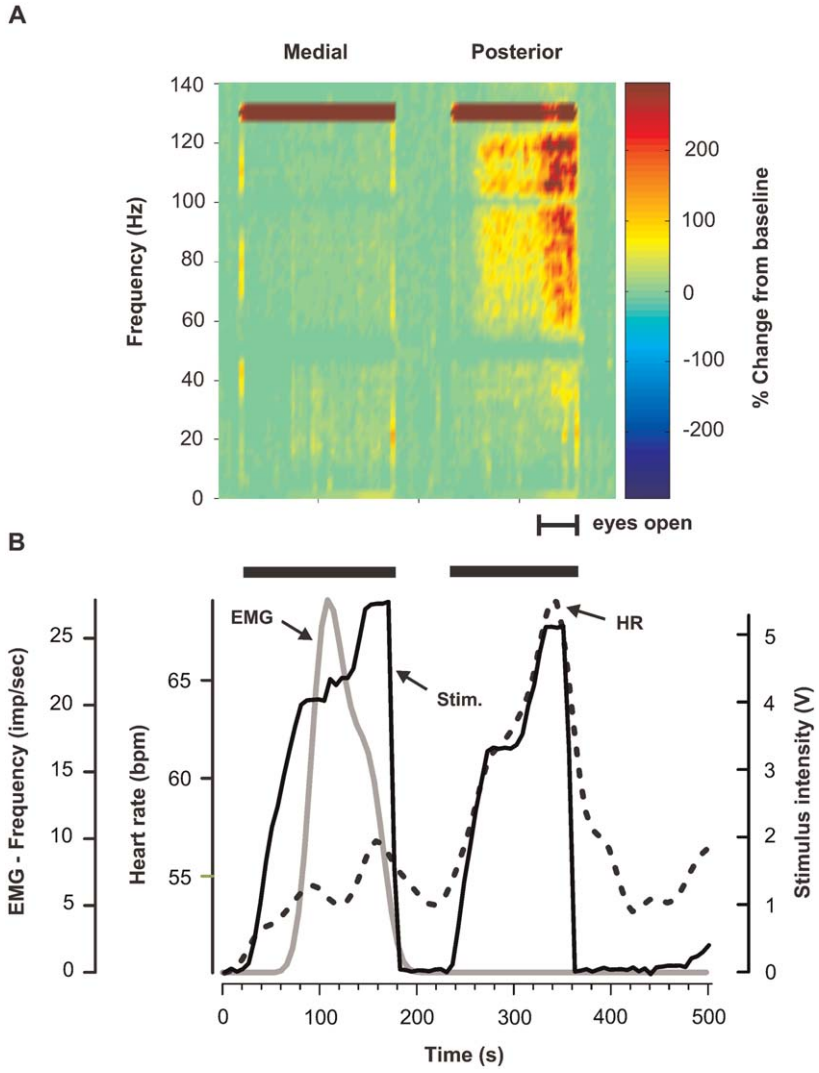

Fig. 4. Electroencephalographic and autonomic arousal. (A) Spectrogram showing the EEG power changes over the ipsilateral sensorimotor cortical area (C3) at different frequencies (*y*-axis) during stimulation of the medial and posterior test-electrode relative to a baseline derived from a 30 s prestimulation period (left hemisphere, 4 mm below AC-PC). While no cortical power changes occur during stimulation of the medial electrode, a strong power increase in the higher gamma band (>60 Hz) can be seen during stimulation of the posterior electrode, which is associated with behavioural arousal. (B) Concurrent changes in heart rate (HR, dashed line; green in the web version) and EMG-activity (grey; blue in the web version). The grey (blue in the web version) line indicates the firing frequency of a single muscle fibre that was recorded from the right m. biceps brachii. The solid black (dashed in the web version) line indicates the strength of stimulation at the medial and posterior electrode, respectively. DBS of the medial trajectory, which did not result in neither cortical nor expressions of behavioural arousal, did not significantly alter the patient's heart rate. The stimulation-related discharge of the muscle fibre indicates current spread to nearby motor fibres in the internal capsule. These fibres were not activated, when the posterior electrode was stimulated. Strong autonomic arousal was associated with cortical and behavioural arousal in this position.

posterior stimulation site, motor-evoked potentials occurred in the contralateral biceps and sternocleidomastoid muscle with a latency of $\sim$9.5 and $\sim$7 ms, respectively (threshold: 5.5 V; see Fig. 2B). With the exception of stimulation-induced changes, no spontaneous movements occurred (as evidenced by clinical evaluation and silent EMG recordings) throughout the operative

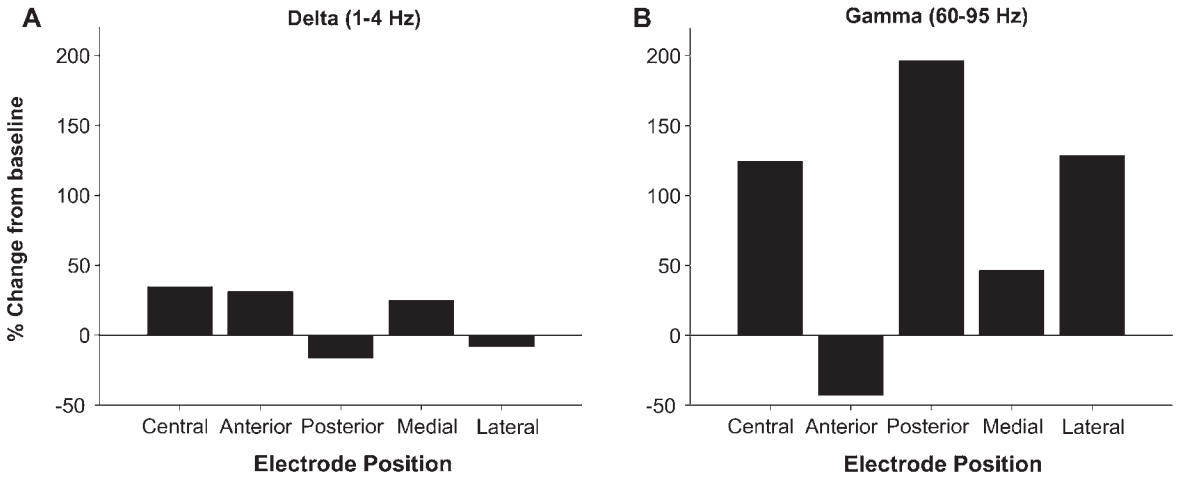

Fig. 5. Stimulation-induced power changes during GPi/NBM DBS. Power changes in the occipital midline EEG (Oz), induced by high-frequency stimulation of different electrode positions in the second (right) hemisphere. Left and right panel show the power changes occurring in the delta and gamma band, respectively.

Table 1. Results of intraoperative deep brain stimulation testing

Hemi-sphere	Depth below AC-PC	Track	Behavioural arousal	EEG arousal	Autonomic arousal	EMG activation
Left	2 mm	Central	No	No	Yes	No
		Anterior	Yes/2.0 V	Yes	No	No
		Posterior	No	No	No	Yes/3.2 V
		Medial	No	No	No	No
		Lateral	No	No	No	No
Left	4 mm	Central	No	No	Yes	No
		Anterior	No	No	Yes	No
		Posterior	Yes/3.0 V	Yes	No	No
		Medial	No	No	No	Yes/3.5 V
		Lateral	No	No	Yes	No
Right	4 mm	Central	Yes/5.0 V	Yes	No	Yes/5.2 V
		Anterior	No	No	No	Yes/6.0 V
		Posterior	Yes/4.5 V	Yes	Yes	Yes/5.5 V
		Medial	Yes/5.7 V	Yes	No	Yes/7.0 V
		Lateral	Yes/7.0 V	Yes	Yes	Yes/7.0 V

course. Table 1 provides a detailed overview of stimulation-related effects for each position of the stimulation electrodes.

Stereotactic reconstruction of the stimulation sites

In order to validate the final electrode positions, a stereotactic CT scan was performed postoperatively and fused with the preoperative MRI. It confirmed the correct position of the DBS electrodes within the GPi, the stereotactic coordinates of the ventral most contacts relative to the mid-commissural point (lateral, anterior, inferior) being $x = 19.6\,\text{mm}$, $y = 2.3\,\text{mm}$, $z = 4.3\,\text{mm}$ for the left and $x = 20\,\text{mm}$, $y = 2\,\text{mm}$, $z = 5\,\text{mm}$ for the right hemisphere (Fig. 6B,E). Correlation of the electrode position with corresponding sections of a stereotactic atlas (Schaltenbrand and Bailey,

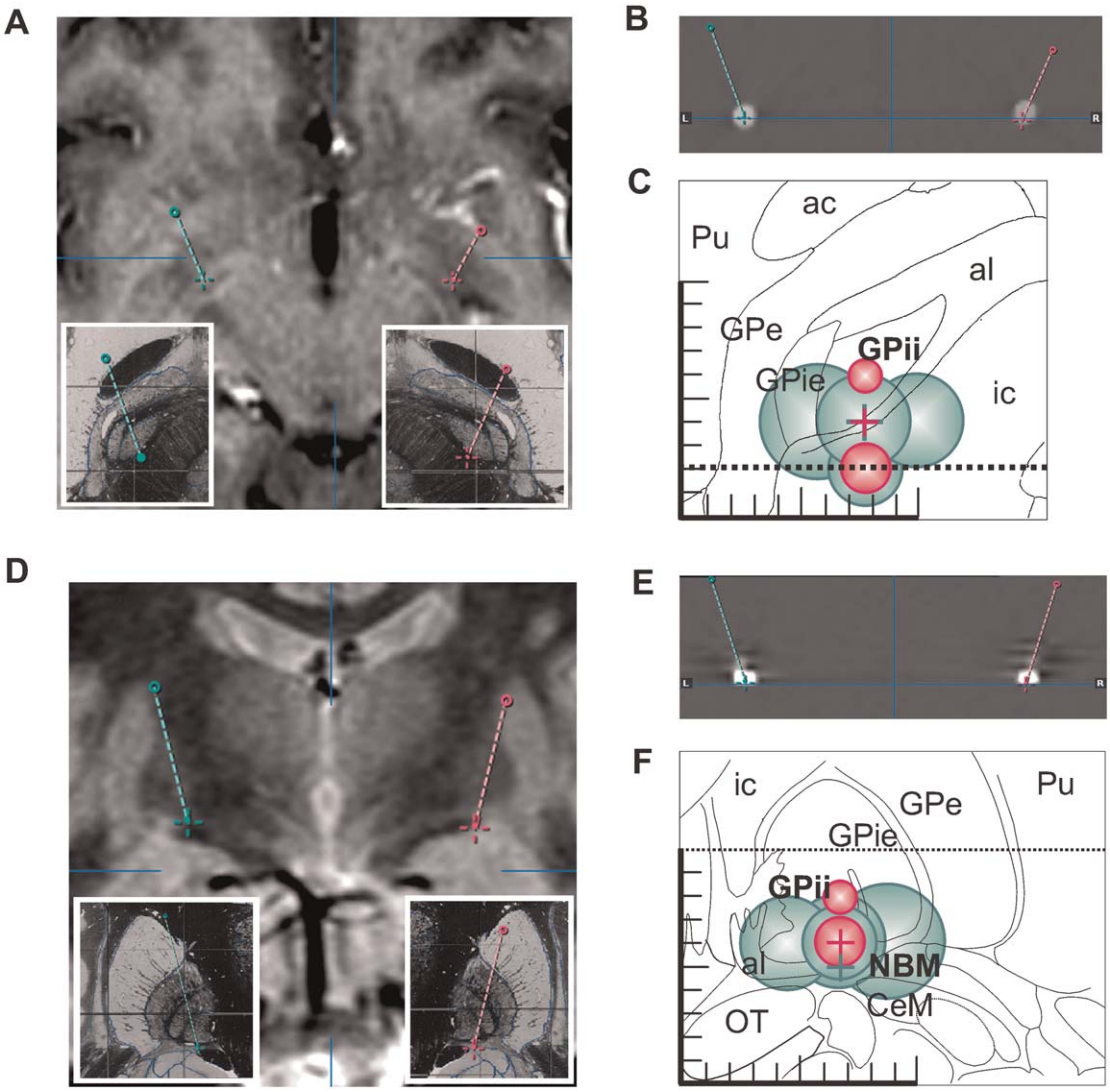

Fig. 6. Stereotactic reconstruction. Stereotactic reconstruction of stimulation sites in the horizontal (A–C) and frontal plane (D–F), respectively. (A) Horizontal T1-weighted MR section with planned target sites at the pallidal base. Insets show the trajectory superimposed on corresponding horizontal sections of the Schaltenbrand/Bailey atlas (Schaltenbrand and Bailey, 1959). (B) Planned trajectory superimposed on a postoperatively acquired horizontal stereotactic CT scan. Note the correspondence with the artefact derived from the implanted DBS electrode. (C) Reconstruction of peripallidal stimulation sites that led to behavioural arousal, with the assumed radial current spread superimposed on a corresponding horizontal atlas section. Note that stimulation results from both hemispheres are superimposed (dark grey, left hemisphere [red in the web version]; light grey, right hemisphere [green in the web version]). Scale bar is 10 mm. Dotted line indicates the midcommissural level. Abbreviations: ac, anterior commissure; al, ansa lenticularis; NBM, ncl. basalis Meynert; CeM, centromedial amygdaloid nucleus; GPe, external pallidal segment; GPie, lateral part of the internal pallidal segment; GPii, medial part of the internal pallidal segment; ic, internal capsule; Pu, putamen. (D) Assumed trajectory course superimposed on a frontal T2-weighted MR section. Note the proximity of the target sites to the optic tract. Insets depict the stereotactic trajectory drawn on a corresponding frontal section of the stereotactic atlas of Schaltenbrand and Bailey (1959). (E) Postoperative stereotactic CT scan, frontal reconstruction. Confirmation of the correct placement of the DBS electrode through superposition of the planned trajectory on the electrode artefact. (F) Reconstruction of arousal-associated stimulation sites and assumed current spread in the frontal plane. Abbreviations as in panel C.

1959) revealed the correct position of the quadropolar electrode with the most inferior contact placed just below the posterolateral pallidal base (Fig. 6).

Postoperative course

The central trajectory was chosen for permanent implantation of the quadropolar DBS electrodes (model DBS 3389, Medtronic Inc., Minneapolis, MN, USA) on both sides. Intraoperatively, bipolar stimulation of the ventral most contact ('0-', cathodal) against the dorsal most contact ('3+', anodal; pulse-width, 60 μs; frequency, 130 Hz) elicited an arousal effect at 5.5 V on the left, but not on the right side. Upon stimulation with higher voltages (>6 V), conjugate eye deviation was observed on the right side. Despite stimulation with even higher intensities (up to 7 V), no capsular affection could be provoked on either side. Upon awakening from anaesthesia after the operation, the patient was interviewed but reported no explicit recollection of the intraoperative arousal episodes. Dystonic head tremor re-occurred immediately. Initially, chronic DBS was started with monopolar stimulation of the most distal contacts ('0-' and '4-' cathodal vs. case+anodal) on both sides (amplitude, 2 V; pulse-width, 90 μs; frequency, 130 Hz) which led to an immediate, but not complete cessation of tremor. Stimulation-induced changes in the level of consciousness could not be reproduced postoperatively because dysarthria occurred at higher intensities (>3.5 V), limiting the range of stimulation. Subsequent follow-up programming sessions revealed that monopolar stimulation of the second most distal contacts ('1' and '5') against the case was more efficient and provided a broader therapeutic window for stimulation. Permanent stimulation of this contact (amplitude, 2.2 V; pulse-width, 90 μs; frequency, 145 Hz) did not lead to any recognizable alteration of the patient's vigilance status or sleep–wake rhythm. However, the patient displayed complete tremor suppression after 2 days (score 0 on the Fahn–Tolosa–Marín Tremor Rating Scale) and near-complete resolution of torticollis (score 4 on the Toronto Western Spasmodic Torticollis Rating Scale) after 1 week. In contrast, discontinuation of DBS resulted in immediate tremor recurrence and was not tolerated because of discomfort from rapidly recurring cervical dystonia. This beneficial stimulation effect has remained stable for more than 24 months, further adding to the notion that bilateral GPi stimulation is effective in suppressing dystonic head tremor.

Discussion

The key novel finding of the present case study is that acute unilateral high-frequency stimulation of the GPi/NBM area evoked a paradoxical arousal reaction, strong enough to transiently reverse general anaesthesia. Our case offered the unusual opportunity to study the functional contribution of a circumscribed region in the subpallidal basal forebrain area to the induction and maintenance of anaesthesia-induced unconsciousness in humans. Considering the difficulty to study the small subcortical sources involved in controlling arousal and behavioural responsiveness physiologically in the human brain, these data are of particular interest. The observations presented in this paper demonstrate an important functional contribution of the GPi/NBM area in a large-scale regulatory network between brainstem and cortex that determines the level of wakefulness and the activation state of the human brain.

An increase of the stimulation amplitude led to a gradual increase in the patient's responsiveness to external sensory stimuli, which covered the full spectrum of arousal levels from complete unresponsiveness (without stimulation), transient behavioural arousal (at subthreshold stimulation values) to persistent behavioural arousal at higher stimulation intensities. Notably, the patient did not show any behavioural signs indicative of conscious awareness during or after these intraoperative arousal episodes, including a lack of explicit recall postoperatively. Thus, electrical stimulation produced a wakeful state without awareness in our patient, to some degree similar to patients that are in a persistent vegetative state following brain injury (Jennett and Plum, 1972). This stimulation-induced dissociation of

wakefulness from awareness is remarkable, since typically, an impairment in arousal is closely linked with an impairment in awareness in most pharmacologically induced and disease-related states of unconsciousness (Laureys, 2005).

Intraoperative arousal effects are only rarely observed, despite the fact that the posteroventral lateral GPi is commonly targeted in surgery for different movement disorders and test stimulation is used intraoperatively in virtually every operation to determine stimulation-induced side effects. However, arousal reactions may be missed because (i) most stereotactic interventions are carried out with the patient awake, (ii) arousal reactions are not specifically provoked and (iii) the NBM is typically spared in pallidal surgery (Vitek et al., 1998). Umbach (1977), in a series of 175 pallidal interventions, reported an incidence of arousal effects seen under high-frequency stimulation below 1%. Therefore, an intraoperative arousal effect may be a rare event during pallidal surgery, possibly attributable to interindividual anatomical differences or to procedural details of surgery and anaesthesia. However, the beneficial clinical course of the described patient indicates that a stimulation-induced arousal reaction occurring during pallidal surgery is not indicative of incorrect electrode placement.

As is the case for any single-case report, a concern is the extent to which the results of the present study may be due to individual peculiarities such as, for example pre-existing structural alterations. There was no evidence in the patient's MRI and CT scans for anatomical abnormalities or damage in the region of interest that could account for the observed stimulation effects. Moreover, typical patterns of cellular activity were regularly encountered during microelectrode recordings from striatal and pallidal sites (Vitek et al., 1998) — with the comparably low firing rates of pallidal units being best explained by the effects of anaesthesia with propofol/remifentanyl (Hutchison et al., 2003). Evidently, one variable of critical importance in the present study may be the level of anaesthesia. It has been demonstrated in animal studies that the threshold for electrical brain stimulation to produce arousal and EEG desynchronization depends on the sleep stage (Grahnstedt and Ursin, 1980). More recently, the critical role of anaesthetic depth for the arousal-threshold has been shown in patients during propofol-induced sedation or general anaesthesia. Whereas i.v. application of epinephrine changed the arousal-level in sedated patients, it had no effect on patients under general anaesthesia (Shin et al., 2004). In our patient, adequacy of surgical anaesthesia was repeatedly ascertained and maintained on a constant level throughout the whole course of the operative procedure, with a propofol dosage typically used for general anaesthesia (Dunnet et al., 1994). There were no autonomic signs of inadequate anaesthesia (lacrimation, flushing, sweating) throughout the operation. With the exception of stimulation-induced increases in responsiveness, the patient did not respond to verbal or tactile stimuli during any part of the operation. Taken together, it seems plausible to attribute the observation of transient reversal of general anaesthesia to the modulatory effects of DBS on an arousal-regulating structure located just below the GPi, rather than to alternative explanations such as individual biovariability in the patient's response to anaesthetic drugs.

Therefore, the discussion will focus on neurofunctional mechanisms and structures underlying the observed stimulation-induced arousal reaction. In this respect, the localization of the stimulating electrode is of critical importance. The conjunction of intraoperative microelectrode mapping and postoperative stereotactic neuroimaging allowed us to determine the precise localization of the stimulation sites within the fibre area between GPi and NBM. We consider first the possible effects of DBS on pallidal outflow which funnels at the base of the pallidum before converging and crossing the posterior limb of the internal capsule (Patil et al., 1998). It is reasonable to assume that a greater number of pallidofugal signals were modulated by DBS in the outflow tracts than at their origin, since these pallidofugal fibre systems are more closely packed than the neurons from which they originate. Amongst other targets in the subthalamic and thalamic areas, the main pallidal outflow projects to the intralaminar thalamic nuclei (Parent and

Parent, 2004), which activate widespread neocortical territories. Inhibition of pallidal input to the intralaminar thalamus, through high-frequency stimulation, could therefore activate the thalamo-cortical system and thus, provide a first plausible interpretation of the non-specific arousal effect and induction of high-frequency rhythms in the EEG. In line with this interpretation, the observed behavioural arousal in our patient resembled very much the, Weckeffekt' originally described by Jung and Hassler who observed partial arousal in mildly sedated patients undergoing stereotaxy upon electrical stimulation of intralaminar thalamic nuclei (Hassler, 1957; Hassler et al., 1960; Jung, 1954; Jung and Hassler, 1960). In addition, the observed electrocorticographic arousal has more recently been described following DBS of the intralaminar thalamus (Velasco et al., 1997, 2006). A recent report demonstrated unexpected awakening from anaesthesia in rats upon attempts to induce lesions in the intralaminar thalamus with ibotenic acid (Stienen et al., 2008). These observations further stress the importance of the intralaminar thalamus as a crucial nodal point that is involved in the regulation of arousal and anaesthetic-induced unconsciousness.

The observed arousal reaction with conjugate gaze and simultaneous opening of both eyes is strongly reminiscent of reticular activation. Stimulation of the mesencephalic reticular formation with 100–300 Hz produces behavioural expressions associated with electrocortical activation and alerting of enduring persistence (Moruzzi and Magoun, 1949). Moreover, reticular stimulation is apt to facilitate intracortical information processing by enhancing stimulus-specific synchrony in the gamma-frequency range (Munk et al., 1996). In our patient, subpallidal DBS induced a clear coordination of lid and eye position. Pathways controlling both the levator palpebrae tonus and the activation of rectus muscles run in close association with the ascending arousal system through the paramedian tegmentum of the upper brainstem (Schmidtke and Buttner-Ennever, 1992). The marked sensitivity of the eyelid position to electrical stimulation in our patient supports the well established intimate relationship between eyelid movements and level of alertness (Kennard and Glaser, 1964). In line with improvements of apraxia of lid opening seen following pallidal DBS (Goto et al., 1997, 2000), our observations demonstrate that descending inputs from the GPi/NBM area are implicated in the supranuclear control of the levator palpebrae tonus. The fact that stimulation was effective in both hemispheres implies that such descending control is exerted bilaterally. Further support for a downstream activation or disinhibition of the brainstem reticular formation may be derived from the observation that sensory stimulation of different modalities, in addition to subthreshold electrical stimulation, led to behavioural arousal. Neurons in the reticular formation of the pons and medulla are innervated by multiple bifurcating and collateral axons of ascending sensory systems. They possess the capacity to respond to stimuli in more than one sensory modality with broad receptive fields (Scheibel et al., 1955) and are thus uniquely positioned to contribute to generalized arousal (Pfaff et al., 2008).

Pallidal efferent pathways descend along the pallidotegmental tract to target cells of the pedunculopontine tegmental (PPT) nucleus (Shink et al., 1997), which is part of the ascending arousal system (Datta and Siwek, 1997; Jones, 2005). Similar to activation of the thalamo-cortical system as described above, DBS-induced inhibition of pallidal outflow could also activate the PPT, which has been considered an interface between the basal ganglia and the reticular formation (Inglis and Winn, 1995).

An alternative interpretation of electrical stimulation near the pallidal base has to take into account the close proximity of neighbouring structures. The current spread using monopolar macrostimulation at current strengths similar to those in this study can roughly be estimated to 2–5 mm (Follett and Mann, 1986; McIntyre et al., 2004). Stimulation may therefore have implicated neighbouring systems in the sublenticular substantia innominata to some extent, in particular the NBM, the widespread cholinergic projections of which have long been implicated in cortical arousal (Detari et al., 1999; Richardson and DeLong, 1988).

The magnocellular basal forebrain complex releases acetylcholine to a number of cortical regions (Jones, 2005). Acetylcholine serves to potentiate neuronal responsivity and thereby facilitate information processing throughout cortical systems (Metherate et al., 1992). In the EEG, electrical stimulation of the NBM induces low amplitude fast oscillations in the gamma-frequency range (Jones, 2004; McLin et al., 2002; Metherate et al., 1992). By providing a steady background of cortical activity, the basal forebrain corticopetal system has been proposed as an important role in mediating cortical arousal and attention (Buzsaki and Gage, 1989). Besides its direct projections to the cerebral cortex, the thalamopetal component of NBM efferents to the reticular thalamic nucleus may provide an alternative pathway for cortical arousal (Heimer, 2000; Steriade and Buzsaki, 1990). Similar to the cholinergic reticulo-thalamic projection, an activation of this route may abolish spindles and slow wave activity in thalamo-cortical systems — leading to a facilitated transthalamic processing of sensory information and an enhancement of high-frequency activities in the EEG (Steriade and Buzsaki, 1990; Steriade et al., 1990). In addition to cortical arousal, autonomic activation has also been demonstrated following electrical stimulation of the NBM (McLin et al., 2002).

The descending NBM projections to sleep–wake related structures in the brainstem may account for the reticular component of behavioural arousal as discussed above (Grove, 1988; Semba, 2000; Semba et al., 1989). Moreover, recent lesioning studies have pointed out the involvement of the basal forebrain cholinergic system in mediating the effects of general (propofol) anaesthesia (Laalou et al., 2008; Pain et al., 2000). It is therefore conceivable, that the arousal effect seen in our patient involved direct stimulation of the posterior sublenticular extension of the NBM (cell group Ch4p) (Mesulam et al., 1983), which consists of several smaller cell aggregates (Zaborszky et al., 2008) of disseminated cholinergic cell groups embedded within the white matter laminae that surround the GP, within the internal capsule or within the ansa lenticularis (Hedreen et al., 1984; Mesulam, 1995; Saper and Chelimsky, 1984). The somewhat diffuse anatomical organization of the posterior Ch4 compartments could help to explain the different arousal thresholds of discrete stimulation sites tested in this study. Importantly, the posterior Ch4 subdivision is commonly confined by two landmark structures which have also been physiologically identified in the present study, that is where the optic tract attaches the internal capsule. Moreover, the centre of gravity of these cell groups is similar to the stereotactic coordinates used in this study (Zaborszky et al., 2008). Surprisingly little is known concerning stimulation effects of the NBM in humans, because it is currently not a target structure for DBS surgery and current surgical strategies aim to spare this neighbouring structure in pallidal surgery (Vitek et al., 1998). Two single case studies of basal nucleus DBS failed to describe clinical or electroencephalographic responses (Engel et al., 2002; Turnbull et al., 1985).

Finally, direct activation of the neighbouring centromedial amygdala or amygdalofugal pathways through volume conduction may constitute yet another possible mechanism subserving the behavioural arousal seen in our patient. The central nucleus of the amygdala is involved in the control of brainstem arousal systems and may increase vigilance by lowering neuronal threshold in sensory systems (Cardinal et al., 2002; Davis and Whalen, 2001). The electrocorticographic response following electrical stimulation of these sublenticular amygdaloid nuclei is in many ways similar, although not identical with the arousal response as elicited by stimulation of the brainstem reticular formation (Belardetti et al., 1977; Feindel and Gloor, 1954). The centromedial amygdala lies approximately 3 mm below the pallidal base (i.e. 7–8 mm below AC-PC). Given the fact that an arousal effect was elicited 2 mm below AC-PC with voltages as low as 2 V on the anterior track of the first stimulated left hemisphere, the possibility that the amygdala was involved in this stimulation effect is not very likely. Furthermore, a recent report of a dislocated pallidal DBS electrode into the left amygdaloid region described mood changes in a patient with dystonia, but did not report on

abnormalities of arousal or behavioural responsiveness associated with unilateral high-frequency stimulation of the amygdala (Piacentini et al., 2008).

Taken together, it seems most plausible to attribute the observed stimulation effect to direct stimulation of the posterior extension of the NBM rather than to a modulation of pallidofugal or amygdaloid pathways and related nuclei. The evidence supporting this conjecture can be summarized as follows. First, disinhibition of the cortico-striato-pallido-thalamo-cortical loop by modulation of increased pallidal outflow, while an attractive hypothesis, lacks experimental validation (Braun et al., 1997; Schiff, 2008; Schiff and Posner, 2007). However, there is strong experimental evidence demonstrating the important role of the NBM in cortical activation (Buzsaki and Gage, 1989; Detari et al., 1999; Dringenberg and Olmstead, 2003; Lee et al., 2005; Metherate et al., 1992; Semba, 1991; Steriade and Buzsaki, 1990). In contrast to the NBM, the GPi cannot be considered a classical site for the induction of cortical activation. Second, the abovementioned routes by which inhibition of pallidal outflow may cause cortical activation are based on the assumption of increased pallidal inhibition — however, our microelectrode recordings clearly show reduced levels of pallidal activity in terms of their discharge rate, rendering this possibility unlikely. Third, the GPi is a rather homogenous nucleus, while the Ch4p compartment consists of several small cell aggregates — potentially explaining the spatial dispersion of effective stimulation sites (Zaborszky et al., 2008). Fourth, the autonomic arousal response is a clue suggesting the involvement of the NBM, since NBM stimulation causes autonomic arousal and alters HR (McLin et al., 2002), whereas GPi stimulation does not (Thornton et al., 2002). Finally, basal forebrain cholinergic neurons (including the cholinergic NBM) have been demonstrated to mediate part of the sedative/hypnotic effects of general anaesthesia with propofol (Laalou et al., 2008; Pain et al., 2000).

Disruption of the arousal-regulatory pathways implicated in the present study may result in abnormally low levels of consciousness (i.e. reduced wakefulness) and problems with arousal, potentially explaining clinically related symptoms like fatigue and hypersomnia which have been reported following pallidal surgery (Hua et al., 2003). Moreover, it has been demonstrated that lesions at the pallidal base may disrupt frontal-subcortical circuits and produce behavioural changes associated with apathy and a reduced vigilance level, such as akinetic mutism (Mega and Cohenour, 1997). A further elucidation of the intimate anatomical and functional relationships between pallidal outflow and neighbouring basal forebrain systems, in particular the NBM, may therefore be of clinical importance.

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