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Desflurane and sevoflurane differentially affect activity of the subthalamic nucleus in Parkinson's disease

Yu-Chen Chen[1,2], Shin-Yuan Chen[1,2], Tsung-Ying Chen[3], Jiann-I Pan[2,4] and Sheng-Tzung Tsai[1,2,*]

[1]Department of Neurosurgery, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation/Tzu Chi University, Hualien, Taiwan, [2]Institute of Medical Sciences, Tzu Chi University, Hualien, Taiwan, [3]Department of Anaesthesiology, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation/Tzu Chi University, Hualien, Taiwan and [4]Department of Medical Informatics, Tzu Chi University, Hualien, Taiwan

*Corresponding author. E-mail: flydream.tsai@gmail.com

Abstract

Background: Desflurane and sevoflurane are commonly used during inhalational anaesthesia, but few studies have investigated their effects on deep cerebral neuronal activity. In addition, the association between subthalamic nucleus (STN) neurophysiology and general anaesthesia induced by volatile anaesthetics are not yet identified. This study aimed to identify differences in neurophysiological characteristics of the STN during comparable minimal alveolar concentration (MAC) desflurane and sevoflurane anaesthesia for deep brain stimulation (DBS) in patients with Parkinson's disease.

Methods: Twelve patients with similar Parkinson's disease severity received desflurane (n=6) or sevoflurane (n=6) during DBS surgery. We obtained STN spike firing using microelectrode recording at 0.5–0.6 MAC and compared firing rate, power spectral density, and coherence.

Results: Neuronal firing rate was lower with desflurane (47.4 [26.7] Hz) than with sevoflurane (63.9 [36.5] Hz) anaesthesia (P<0.001). Sevoflurane entrained greater gamma oscillation power than desflurane (62.9% [0.9%] *vs* 57.0% [1.5%], respectively; P=0.002). There was greater coherence in the theta band of the desflurane group compared with the sevoflurane group (13% *vs* 6%, respectively). Anaesthetic choice did not differentially influence STN mapping accuracy or the clinical outcome of DBS electrode implantation.

Conclusions: Desflurane and sevoflurane produced distinct neurophysiological profiles in humans that may be associated with their analgesic and hypnotic actions.

Keywords: deep brain stimulation; desflurane; microelectrode recording; Parkinson's disease; sevoflurane; subthalamic nucleus

Editor's key points

- Direct comparison of intracerebral neuronal recordings under desflurane or sevoflurane anaesthesia has not been reported in humans.
- Microelectrode recordings under equipotent desflurane or sevoflurane anaesthesia provide an opportunity to elucidate how these anaesthetics modulate neuronal firing.
- Anaesthetic choice did not differentially influence subthalamic nucleus mapping accuracy or clinical outcome of deep brain stimulation electrode implantation.
- Desflurane and sevoflurane produced distinct neurophysiological profiles in human subthalamic nucleus that may be associated with their analgesic and hypnotic actions.

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Desflurane and sevoflurane are commonly used volatile anaesthetics[1]; their clinical potencies are measured in minimum alveolar concentration (MAC) multiples, an indication of anaesthetic effects on the spinal cord.[2] Although it is known that MAC changes with age,[3] it is not clear whether the same equipotent MAC for different inhalational anaesthetics results in similar neurophysiological effects. Studies using the surgical pleth and bispectral indices to evaluate analgesia and hypnosis indicate different required doses for desflurane and sevoflurane.[4,5] In addition, EEG in humans and rodents has shown inconsistent effects of these volatile anaesthetics on grouped neuronal activity. For example oscillations spanning from theta, alpha, to high gamma bands each correlate with loss of consciousness and analgesia.[6,7] However, direct comparison of intracerebral neuronal recordings under desflurane or sevoflurane anaesthesia has not been reported in humans.[8,9]

Deep brain stimulation (DBS) is an effective therapy that improves motor symptoms in Parkinson's disease (PD). Patients are usually awake and under local anaesthesia for the procedures to ensure accurate electrophysiological mapping of the subthalamic nucleus (STN) using microelectrode recording. However, patients that experience off-medication symptoms such as painful dystonia and respiratory distress may have difficulty with this lengthy surgical procedure, and awake intracerebral recording may induce nervousness. For these reasons general anaesthesia is an alternative choice, with some studies showing similar effectiveness and safety as local anaesthesia.[10–15] Microelectrode recording under equipotent desflurane or sevoflurane anaesthesia provides an opportunity to elucidate how inhalational anaesthetics modulate neuronal firing and oscillation within the basal ganglia.

The roles of STN and basal ganglia in the mechanisms of inhalational anaesthetic agents and loss of consciousness are not yet well delineated. The effects of desflurane and sevoflurane on DBS and STN firing activity also have not been directly compared. We sought to compare the clinical efficacy of DBS using desflurane or sevoflurane anaesthesia, and to investigate the neurophysiological properties of STN neurones for each anaesthetic. On the basis of previous findings, we hypothesised that desflurane and sevoflurane would entrain STN oscillations in different power spectra.

Methods

Patient data

This study was approved by the institutional review board of Tzu Chi General Hospital, Hualien, Taiwan (IRB 097–32). From May 2014 to June 2016, written informed consent was obtained and data were collected from 12 patients (eight females and four males; mean age, 58.4 [9.1] yr) with PD who underwent DBS electrode implantation. Patients with a diagnosis of PD were recruited based on our prospective follow-up from patients with a diagnosis of PD scheduled for microelectrode recording under general anaesthesia. These patients received desflurane (n=6) or sevoflurane (n=6) during microelectrode recording at the discretion of the anaesthetist. All patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) under three different conditions: preoperative on medication (Med on), preoperative off-medication (Med off), and postoperative with DBS (DBS on). Details regarding the evaluation procedures (including UPDRS part II and part III) were as described.[11,12]

Anaesthetic procedure

Patients received desflurane or sevoflurane anaesthesia with tracheal intubation. Propofol (1–2.5 mg kg^{-1}) and a neuromuscular blocking agent (0.6–1.5 mg kg^{-1} rocuronium or 0.15–0.2 mg kg^{-1} cisatracurium) were administered to induce anaesthesia. After the patient lost consciousness, the anaesthesiologist stopped the propofol infusion and started desflurane or sevoflurane to maintain unconsciousness. The MAC was maintained at 1.0–1.2 before neurophysiological recordings to avoid inadvertent patient movement or awareness. Anaesthetic concentration was steadily decreased every 30 min and was kept stable at 0.5–0.6 with age-adjusted MAC during microelectrode recording (Fig. 1). End-tidal anaesthetic concentration was 0.7–0.8 when MAC was maintained at 0.5–0.6. After successful STN mapping, MAC was resumed at 1.0–1.2, and the electrodes were implanted. Intravenous anaesthetics and analgesics that dampen STN firing were avoided during surgery. We continuously monitored HR and averaged HR every 20 min at different steady-state MAC levels.

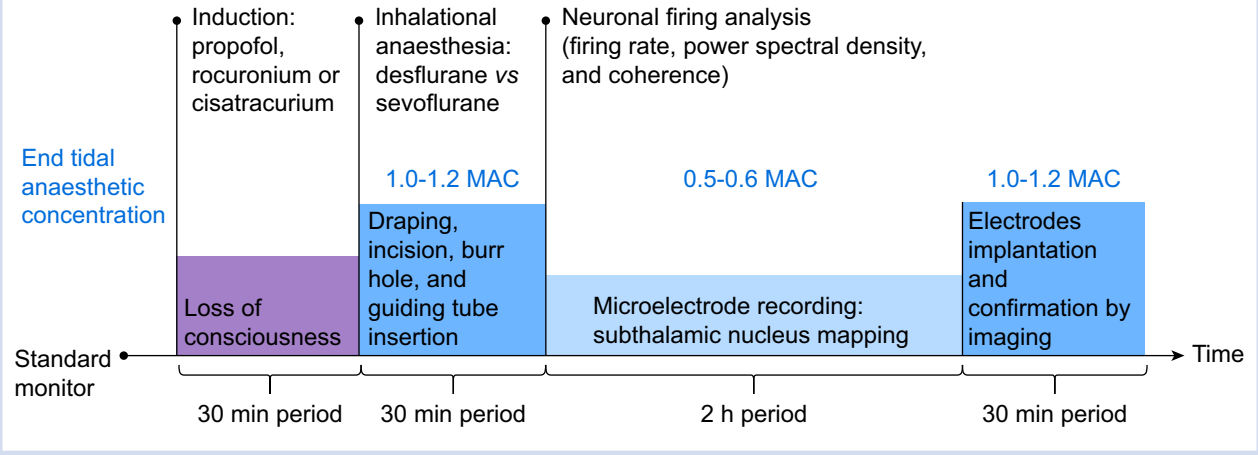

Fig 1. Study procedures. Microelectrode recordings were obtained and analysed for neuronal characteristics (firing rate, power spectral density, and coherence) at 0.5–0.6 minimal alveolar concentration (MAC).

Patients with a diagnosis of PD did not receive opioids or beta blockers preoperatively.

Microelectrode recording

Microelectrode recording procedures have been described.[11] Starting coordinates for recording were 10 mm above the planned STN coordinates. The microelectrode was advanced in 200–500-μm steps and was paused at sites with robust neuronal firing. The final trajectory for electrode implantation was selected based on the length of the STN recording and the presence of kinematic responses.[16]

Spike activity analysis and power spectrum density estimation

Spike trains were quantified as amplitude >3.5 standard deviations every 1 s of recording. The firing rate was evaluated over the entire session using 1-s bins. In order to calculate effects of desflurane and sevoflurane, we analysed percentage change of firing rates (e.g. firing in dorsal STN in sevoflurane − firing in dorsal STN in desflurane/firing in dorsal STN in desflurane %). To analyse neuronal oscillations, we utilised point processes to describe spike trains. Point processes were encoded by the time the spike event occurred and the spectral analysis could be directly performed.[17] The oscillation characteristics were evaluated using the power spectrum density (PSD) of the spike train with Thomson's multi-taper method.[18,19] Parameters included the time half bandwidth product with 3, a length equal to the number of samples in 3 s, and 50% overlap between windows that produced 1/3 Hz spectral resolution. Each PSD was normalised by integrating the 3–100 Hz band (excluding the 48–52 Hz band) to obtain relative power within the band. We then determined the normalised spectral power from theta (3–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–100 Hz) band ranges in each trace. To analyse the topographical distribution of STN spike properties, the STN was divided into dorsal (0–50%) and ventral (50–100%) components.

Background activity

We took the raw trace segments from 0.5 ms before to 2.5 ms after each spike timestamp and replaced them with a random spike-free 3 ms consecutive signal from a random location within the same recorded trace.[19,20] The reconstructed novel trace was defined as background activity, which was extracted using a full-wave rectification method that removed the DC component and rapid oscillations. Low frequency oscillations in the rectification data of the frequency domain could be clearly observed.[21,22]

Coherence between spike and background activity

The degree of frequency relationships between spike trains and background activity was evaluated using coherence analysis.[19 20] Coherence is a function of the PSD of x and y (P_{xx} and P_{yy}, respectively) and the cross PSD of x and y (P_{xy})[23,24]:

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$

The coherence function used the Welch method with a Hanning window (2 s sample numbers) and 50% overlap between windows that produced a 0.5 Hz spectral resolution. The significant coherence level in analyses was calculated as

$$limit = 1-((1-\alpha))^{1/(N-1)}$$

We separately analysed the four frequency bands. Therefore, Bonferroni test significance was adjusted to

$$limit = 1-((1-\alpha)/n)^{1/(N-1)}$$

where α=0.99, n denotes the number of independent frequencies under investigation and N is the number of 2 s consecutive windows used for the coherence calculation.[25] This allows for a confidence value of P<0.025 when rejecting the null hypothesis of non-significant coherence. We compared the average of the ratio of significant coherence, which was computed at every recording depth for the desflurane or sevoflurane group.

Statistical analysis

No formal statistical power calculation was conducted to guide sample size. Statistical analyses were performed using SPSS software 21 (IBM Corp., Armonk, NY, USA) and MATLAB 2018 (The Mathworks, Inc., Natick, MA, USA). The Kolmogorov–Smirnov test was used to test the normality distribution of continuous variables. If the data were normally distributed, Student's t-test was used to compare the two anaesthetics. Wilcoxon rank-sum test was performed for variables without a normal distribution. Significance was set as P<0.05 (two-tailed) and corrected based on number of comparisons. We used false discovery rate (FDR) to correct

Table 1 Subject characteristics of Parkinson's disease patients undergoing deep brain stimulation under desflurane or sevoflurane anaesthesia. Data are expressed as frequencies for categorical variables, mean (range) for age at onset, age at surgery, and disease duration, and mean (standard deviation) for height, weight, and BMI.

	Desflurane group (n=6)	Sevoflurane group (n=6)
Age at onset (yr)	49 (40–56)	49.5 (36–64)
Age at surgery (yr)	58 (46–68)	59 (44–69)
Sex (male/female)	3/3	1/5
Height (cm)	163 (156–167)	162 (159–167)
Weight (kg)	60.7 (48–75.6)	61 (50–83)
BMI (kg m^{-2})	22.9 (19.3–31.0)	23.0 (19.2–31.2)
Disease duration (yr)	10 (8–15)	9 (5–15)
ASA physical status (1/2/3)	0/5/1	1/4/1

significance for multiple comparisons in PSD over different frequency band oscillations to prevent compounding of the type I error. We also used Bonferroni *post hoc* testing to correct significance for coherence under multiple comparisons because it was suitable for independent and small size data. Spearman correlations were used to estimate the strength of association between STN neuronal activity parameters (spectral density of the four band powers) and clinical scores collected using UPDRS (rigidity, bradykinesia, axial symptoms, and tremor) during Med off. $P<0.05$ was used to indicate a significant correlation. Data are presented as mean (standard deviation).

Results

Patient characteristics are shown in Table 1, with no significant differences between the two groups. Intraoperative recordings from 45 microelectrode recording units under desflurane anaesthesia and 57 units under sevoflurane anaesthesia were analysed for spontaneous STN unit activity. Both groups showed similar motor disabilities before bilateral STN-DBS, which were all significantly improved by DBS treatment (Table 2). STN-DBS effectiveness did not differ between groups. Both anaesthetics produced similar decreases in HR from the conscious baseline to at 1.0–1.2 MAC (Supplementary Fig. S1). However, HR in the sevoflurane group was significantly higher than HR in the desflurane group at 0.5–0.6 MAC.

Spike firing rate, power spectral density, and coherence

We evaluated neuronal spike firing rate characteristics (Table 3). The mean firing rates were 47.4 (26.7) Hz and 63.9 (36.5) Hz ($P<0.001$) for desflurane and sevoflurane, respectively. Regional STN analyses showed higher firing rates in the ventral STN than the dorsal STN for the desflurane group ($P<0.001$), but no differences for the sevoflurane group ($P=0.209$). The dorsal and ventral STN firing rates under sevoflurane anaesthesia were 62.8% and 11.30% greater than those under desflurane anaesthesia ($P<0.001$ and $P=0.013$, respectively).

We examined the oscillatory features of the microelectrode recording signals using PSD, which was divided into theta, alpha, beta, and gamma band oscillations. No significant difference was observed at the theta, alpha, and beta bands (Fig. 2). However, the gamma band power was higher for sevoflurane than for desflurane ($P=0.002$). There was small insignificant increase in theta band power for desflurane anaesthesia (8.2% [0.5%]) compared with sevoflurane anaesthesia (7.0% [0.3%]) ($P=0.051$). We further analysed PSD within the dorsal and ventral STN. Only the gamma frequency oscillation in dorsal STN was higher in the sevoflurane group ($P=0.004$). Beta frequency oscillation did not differ between groups.

Coherence measures the correlation between spiking neuronal activity and background oscillations within a frequency domain. We compared the proportion of coherence that were above the significance level (95% interval) between desflurane and sevoflurane in each power band. There was a higher proportion of significant coherence within the theta frequency for desflurane anaesthesia (13.3% in desflurane *vs* 6.1% in sevoflurane group). In contrast, there was greater coherence within the alpha, beta, and gamma frequencies

Table 2 Preoperative and postoperative medication and deep brain stimulation effectiveness between desflurane and sevoflurane groups. Data are expressed as mean (95% CI). The Student's t-test was used for statistics for desflurane and sevoflurane under Med off, Med on, and DBS on.

		Part II	Part III	Tremor	Rigidity	Bradykinesia	Axial	H&Y stage
Med off	DES	24.2 (8.1)	46.3 (10.8)	7.50 (7.28)	6.33 (0.97)	20.5 (3.4)	10.0 (1.8)	3.33
	SEV	21.0 (4.3)	45.8 (6.7)	8.67 (5.35)	8.00 (3.20)	19.0 (3.6)	8.8 (1.3)	3.33
Med on	DES	9.7 (3.7)	23.0 (3.4)	1.17 (4.86)	3.00 (0.72)	11.5 (2.3)	6.2 (1.3)	2.50
	SEV	5.8 (1.7)	20.2 (4.9)	1.00 (0.72)	5.00 (2.68)	10.3 (3.5)	3.2 (1.4)	2.42
Improvement[a] (%)	DES	59.8 (11.4)	48.2 (9.1)	56.6 (36.0)	49.8 (17.4)	43.2 (10.4)	36.0 (16.9)	
	SEV	70.3 (9.8)	54.6 (12.0)	85.0 (14.8)	41.0 (15.8)	45.7 (12.4)	65.0 (15.5)	
DBS on	DES	11.5 (3.9)	25.3 (7.5)	3.33 (3.15)	3.33 (1.88)	12.3 (1.3)	5.3 (1.6)	2.56
	SEV	11.0 (3.0)	24.5 (6.3)	3.67 (4.55)	3.33 (2.51)	11.5 (2.8)	5.2 (2.0)	2.50
Improvement[b] (%)	DES	45.1 (10.4)	47.3 (10.2)	47.0 (34.6)	59.5 (35.4)	44.4 (13.4)	41.8 (14.2)	
	SEV	42.1 (24.2)	45.7 (14.1)	62.2 (32.8)	56.7 (22.4)	38.6 (10.8)	40.3 (24.3)	
P-value	Med off	0.26	0.47	0.40	0.18	0.28	0.16	0.50
	Med on	0.05	0.19	0.40	0.09	0.30	0.01	0.30
	DBS on	0.42	0.38	0.32	0.14	0.30	0.23	0.34
	Improvement[a]	0.10	0.21	0.09	0.24	0.38	0.03	
	Improvement[b]	0.17	0.31	0.32	0.24	0.45	0.42	

[a] Improvement (%): Med off scores − Med on scores/Med off scores × 100%.
[b] Improvement (%): Med off scores − Med off DBS on scores/Med off scores × 100%. CI, confidence interval; DBS on, deep brain stimulation on; DES, desflurane; H&Y, Hoehn and Yah; Med off, medication off; Med on, medication on; SEV, sevoflurane; UPDRS, unified Parkinson's disease rating scale.

Table 3 Comparison of firing rate in dorsal and ventral subthalamic nucleus regions between desflurane and sevoflurane groups. Data are expressed as mean (95% confidence interval).

	Desflurane group (n=6)	Sevoflurane group (n=6)	P-value	Different percentage[a] (%)
Dorsal	40.4 (37.9–42.7)	65.8 (60.8–70.8)	<0.001	62.8
Ventral	53.8 (49.9–57.7)	61.0 (57.4–64.6)	0.013	11.3
P-value	<0.001	0.209		

[a] $([Mean_{Sevoflurane\ Group} - Mean_{Desflurane\ Group}]/Mean_{Desflurane\ Group}) \times 100\%$.

under sevoflurane anaesthesia (desflurane *vs* sevoflurane; alpha, 12.6% *vs* 18.2%; beta, 7.4% *vs* 15.7%; gamma, 8.3% *vs* 12.9%) (Fig. 3).

Spearman correlations between individual power bands and motor disabilities indicated a strong negative correlation between axial scores and theta frequency oscillation under sevoflurane anaesthesia (ρ=−0.97, P=0.033). No correlations were found between individual band power and tremor, rigidity, or bradykinesia severity for either anaesthetic.

Discussion

Desflurane and sevoflurane, both halogenated ethers, share similar chemical structures, and would presumably produce comparable effects on neuronal activity. However, 0.5–0.6 MAC reduced STN neurone firing rates under desflurane compared with sevoflurane anaesthesia. Under sevoflurane anaesthesia, gamma frequency oscillations predominated. In contrast, similar PSD and coherence analyses indicate that desflurane anaesthesia entrained the lower gamma power band and higher theta power band. These neurophysiological phenomena support previous research[4,5] indicating that desflurane produces stronger effective analgesia than sevoflurane anaesthesia. In addition, patients receiving desflurane had significantly lower HRs compared with those receiving sevoflurane at 0.5 MAC. This suggests that these two anaesthetics have different neuro-autonomic effects. Although the precise underlying mechanisms of inhalational anaesthesia are not yet fully understood, it is essential to establish the neuronal networks that underlie anaesthetic hypnosis, analgesia, and immobility.[26]

We analysed PSD to evaluate the effects of desflurane and sevoflurane on oscillation frequency bands within the STN. Desflurane produced stronger power and coherence over the theta frequency oscillation. Increased theta band oscillations have been reported during deep sleep or deep desflurane anaesthesia,[27,28] and surgical pleth and bispectral indices suggest that desflurane produces analgesia and hypnosis more effectively than sevoflurane.[4,5] Therefore, the increased theta band oscillation and greater proportion of coherence within the theta band under desflurane anaesthesia might indicate the theta band oscillation as a neurophysiological biomarker of analgesia and hypnosis. In contrast, sevoflurane produced a higher power gamma band oscillation in the dorsal STN and a greater proportion of coherence over the gamma band. Recordings from STN have been shown to correlate with painful stimuli in patients with a diagnosis of PD.[29] These physiological observations using microelectrode recording are similar to findings showing that pain intensity was encoded by gamma oscillations in EEG over the prefrontal cortex.[30] Neuronal oscillations in STN correlate with cortical activity from EEG in patients with a diagnosis of PD.[31] These data suggest that the association of sevoflurane with reduced analgesia and gamma oscillations might be used as a surrogate marker for pain perception during volatile anaesthesia. Taken together, we propose that at 0.5–0.6 MAC desflurane anaesthesia produces more analgesia and hypnosis than sevoflurane.

We did not observe a difference in beta band oscillation between the two anaesthetics. The pathologically enhanced beta band oscillation activity across the cortico-basal ganglia pathway is a neurophysiological characteristic associated with PD, and beta band oscillation has been suggested for locating the sensorimotor STN.[32–34] This lack of difference in beta band oscillations between groups indicates that anaesthetic choice would not reduce STN identification accuracy and proper electrode implantation.

DBS produced similar improvements in motor capabilities for each anaesthetic. Correlations assessing the association between neurophysiological and clinical parameters have only identified correlation between axial symptoms and beta band oscillations under sevoflurane anaesthesia. Correlations between neurological and neurophysiological PD characteristics have been shown.[35–37] Given the implication that volatile anaesthetics modulate inherent STN neuronal firing and oscillations, we did not uncover a significant relationship between band power and motor disabilities.[38]

Although we found that desflurane and sevoflurane progressively decreased HR to similar levels at 1.0–1.2 MAC, desflurane resulted in a larger HR reduction at the 0.5–0.6 MAC level. Previous studies have shown that desflurane produces more neurocirculatory responses, whereas sevoflurane exhibits more stable haemodynamics, and the change of HR remained steady between MAC 1.0–1.2 and 0.5–0.6.[39,40] In addition, desflurane increased basal HR when we increased MAC to higher steady state (1.0–1.2 MAC). HR has been used as a surrogate for analgesia quantification using surgical stress index or analgesia nociception index.[41,42] Previous work also explored the interaction between HR and brain oscillations.[43] Whether the differential effect on HR and autonomic nervous system is directly from the volatile anaesthetic or via the change of brain oscillation warrants further research to identify the relationship. This suggests that either oscillatory power from brain recordings or a HR-based index provides better analgesia monitoring.

This study had several limitations. First, patients were not randomised to the desflurane and sevoflurane groups. Despite this, the groups were well matched in disease severity, including motor disability and psychiatric features, which should minimise confounding effects in the correlations between phenotypic differences and neurophysiological features. Second, the study did not include a quantitative analysis of neuronal characteristics under MAC levels of anaesthesia within the same patients. The surgical and recording procedures and

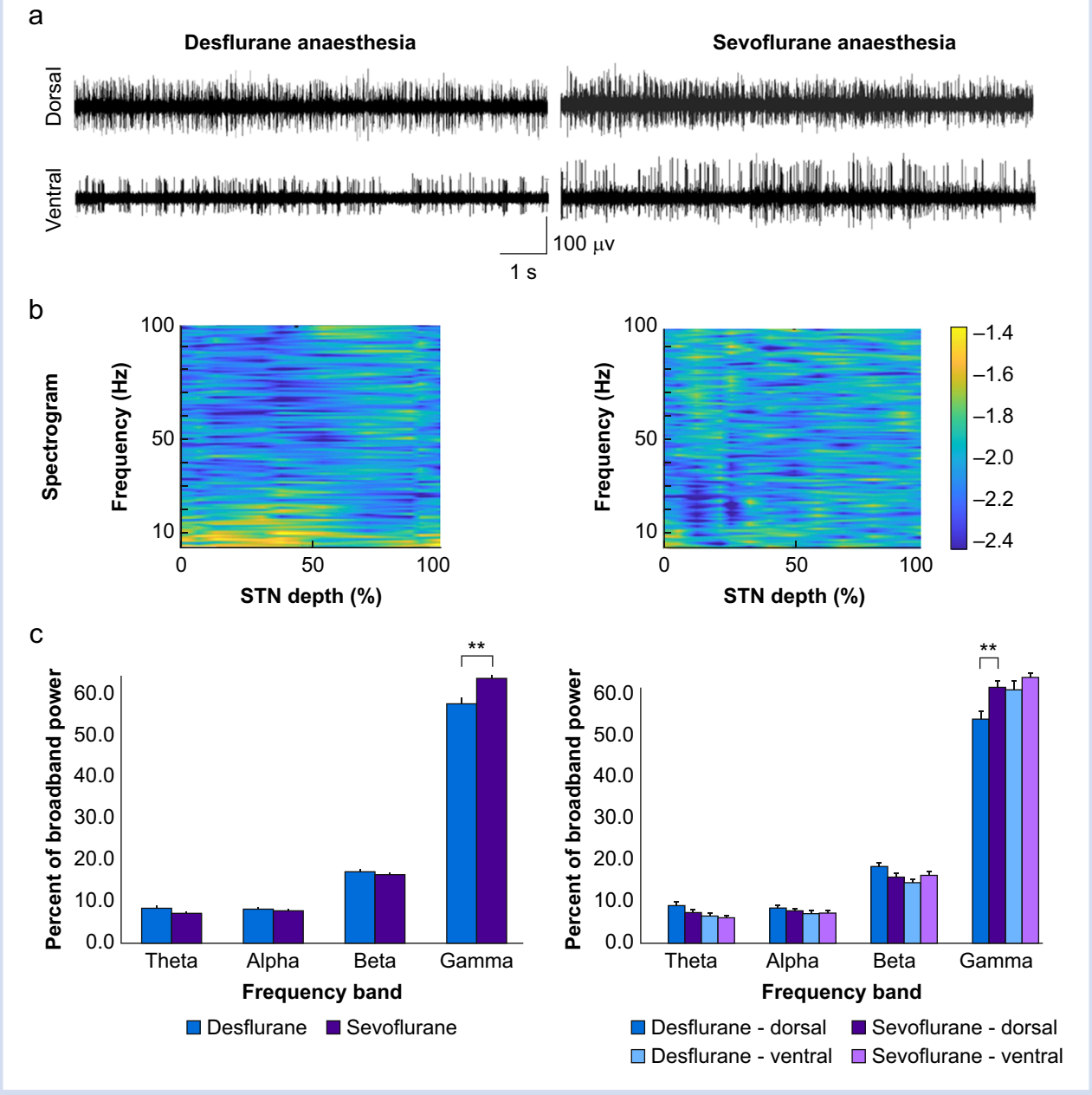

Fig 2. Two illustrative cases and group analysis of power spectral density (PSD) in the subthalamic nucleus (STN). (a) Two representative microelectrode recording data from the dorsal and ventral STN under each anaesthetic. (b) Topographical spectrogram changes revealed higher values in the gamma band oscillation in the sevoflurane group. (c) Comparison of each frequency band between desflurane and sevoflurane (45 microelectrode recording units under desflurane and 57 units under sevoflurane) revealed a significant effect of anaesthetics on the gamma band in the dorsal STN by Wilcoxon rank-sum test with two-tailed. **$P<0.01$ between desflurane and sevoflurane groups.

concentration and dose of the anaesthetics remained the same for each patient during microelectrode recording to reduce confounders. This suggests that the findings are secondary to differences between desflurane and sevoflurane. Third, the relatively small study size limits our ability to detect small neurophysiological differences between anaesthetics.

In conclusion, anaesthesia with desflurane or sevoflurane is feasible for STN mapping and implanting DBS electrodes to ensure optimal clinical outcomes. However, desflurane and sevoflurane differentially influenced STN firing activity and entrained different brain oscillation bands that may contribute to their hypnotic and analgesic actions. The HR findings further suggest that these anaesthetics do not share similar physiological effects, even at equivalent MAC. Future studies using intraoperative microelectrode recording parameters under inhalational anaesthesia should be cautiously used to design stimulation strategies or predict STN-DBS benefits.

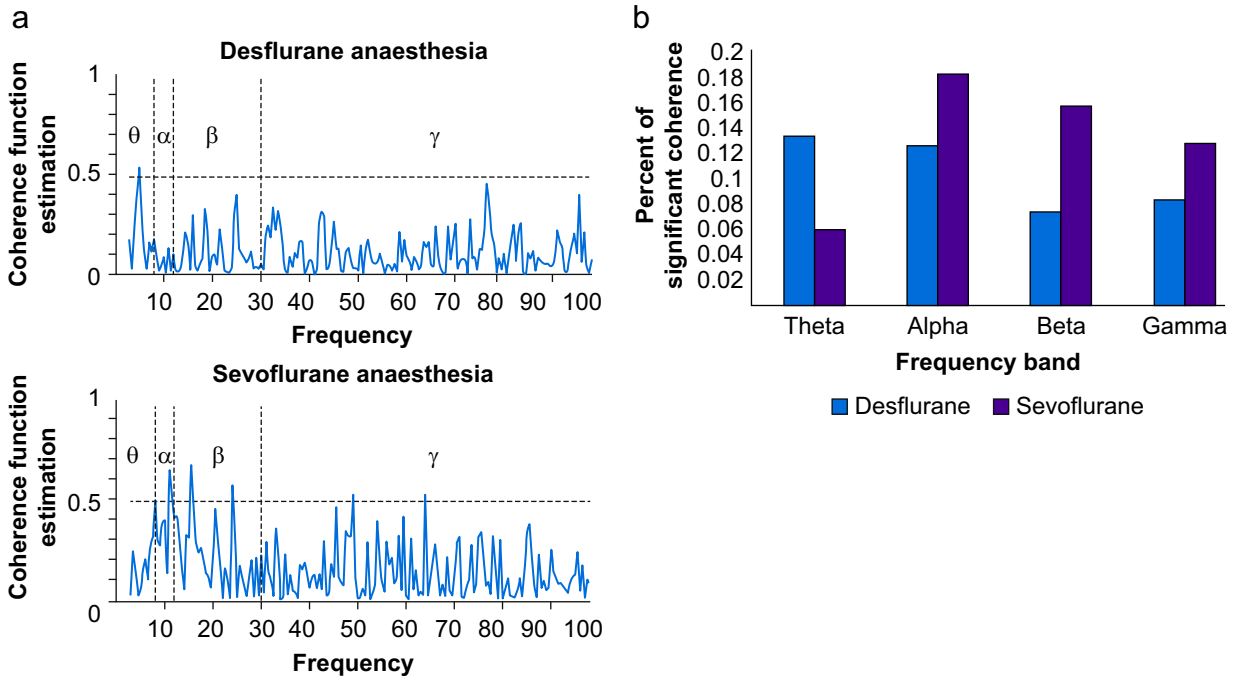

Fig 3. Coherence comparisons between desflurane and sevoflurane groups in each power band. (a) Coherence was quantified as spike activity significantly correlated with the background activity, with the dashed line indicating significant coherence at a 95% confidence interval. (b) Comparison of the proportion of significant coherence within each power band revealed that desflurane produced a greater proportion of significant coherence in the theta band and trended towards lower coherence in the gamma band compared with sevoflurane.

Authors' contributions

Study design/planning: all authors
Data analysis design and execution: YCC, STT
Data analysis review and critique: SYC, TYC, STT
Writing of the first draft: YCC, STT
Manuscript review and critique: SYC, TYC, JIP, STT
All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.09.041.

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