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Electrographic seizures during low-current thalamic deep brain stimulation in mice

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Abstract

Background: Deep brain stimulation of central thalamus (CT-DBS) has potential for modulating states of consciousness, but it can also trigger electrographic seizures, including poly-spike-wave trains (PSWT).
Objectives: To report the probability of inducing PSWTs during CT-DBS in awake, freely-moving mice.
Methods: Mice were implanted with electrodes to deliver unilateral and bilateral CT-DBS at different frequencies while recording EEG. We titrated stimulation current by gradually increasing it at each frequency until a PSWT appeared. Subsequent stimulations to test arousal modulation were performed at the current one step below the current that caused a PSWT during titration.
Results: In 2.21% of the test stimulations (10 out of 12 mice), CT-DBS caused PSWTs at currents lower than the titrated current, at currents as low as 20 μA.
Conclusion: Our study found a small but significant probability of inducing PSWTs even after titration and at relatively low currents. EEG should be closely monitored for electrographic seizures when performing CT-DBS in both research and clinical settings.

Keywords: Seizure, Deep-brain stimulation, Thalamus, Electroencephalography, Electric stimulation

Introduction

Deep brain stimulation of central thalamic nuclei (CT-DBS) is an effective technique for regulating brain arousal: it has helped to speed re-

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covery from minimally conscious states (MCS) in humans [1, 2], reverse the effects of anesthesia in non-human primates (NHPs) [3–5], and enhance cognitive abilities in awake rodents and NHPs [6–9]. The neurons in the central thalamus are uniquely positioned to modulate brain arousal states as they send excitatory projections to the striatum and frontal and association cortices, and traumatic brain injuries involving central thalamic nuclei result in a variety of disorders of consciousness, including MCS [10].

Electrical stimulation of the central thalamus can also induce electrographic seizures, like spike-wave discharges (SWDs), in cats [11], NHPs [12, 13], and humans [14]. In NHPs, CT-DBS has also been reported to induce a "vacant stare" that resembles absence seizures [15]. SWDs are characterized by a series of spikes and waves observed in the electroencephalogram (EEG) or local field potentials and are associated with absence seizures in humans [16]. SWDs are not only produced by central thalamic electrical stimulation but also by optogenetic stimulation of this area [17]. In this study we report the probability of inducing electrographic seizures during test stimulations performed at the current one step below the current that caused a electrographic seizure during titration.

Methods

Animals and Surgery

All experiments were performed in strict accordance with MIT IACUC (protocol # 2303000480) and National Institutes of Health guidelines. C57BL/6J mice (8–46 weeks) were implanted (n = 12, 7 male) under isoflurane anesthesia (2.5% induction, 1.8% maintenance with 1 L/min oxygen) with bipolar tungsten electrodes for stimulation ($\varnothing = 125$ μm, P1) aimed at the central thalamus (AP: -1.0 to -1.4, ML: $\pm$0.7, DV: -2.6 to -2.7; implanted impedances $\leq$200 kΩ), and stainless steel screws for EEG recording (8209, Pinnacle) were implanted over the frontal (AP: +1.5, ML: +0.7) and parietal (AP: -3.0, ML: -1.3) cortices, with ground and reference screws over the cerebellum. Extended-release buprenorphine (1 mg/kg) was given for post-operative analgesia. Mice were individually housed with a 12-hr light-dark cycle and were provided food and water ad libitum.

Recording and Stimulation

The EEG was recorded at 2713 Hz and band-passed (0.5–500 Hz; Neuralynx). Video was also recorded. Constant current stimulation (STG-8000, Multichannel Systems) consisted of biphasic, cathodal first, charge-balanced, 100-μs square pulses separated by a 100-μs isoelectric period and were applied either unilaterally or bilaterally [18].

Experiments

The animals recovered for three days after surgery, and then were habituated to the recording cage. The animals were given food and sugar pellets during habituation and experiments. Experiments were performed during the animals' light phase and lasted 4–80 minutes. Titration consisted of 10-s stimulation periods separated by 10-s off periods at gradually increasing current steps (1, 5, 10, 20, 30, 50, 80, 100, 150, and 200 μA) until a poly-spike-wave train (PSWT) was observed or 200 μA was reached (Fig. 1A, left). 60-s test stimulations, separated by 120-s off periods, were performed at the current one step below the current that caused a PSWT (Fig. 1A, right). Titration and test stimulations were repeated at each of five frequencies (1, 10, 50, 100, and 200 Hz). Animals were awake and freely moving during the experiments.

Histology

After experiment completion, electrolytic lesions were created using 20 μA DC current for 10 s while the mice were under isoflurane anesthesia (1.8%). Later, the mice were deeply anesthetized and perfused with 10% formalin. The brains were sliced in 50-μm sections, mounted using DAPI-containing media, and imaged using a fluorescence microscope and the Zen Blue software (Zeiss). To locate the electrode tip, co-registration to the Allen Mouse Brain CCF [19] was performed in MATLAB using open-source software [20].

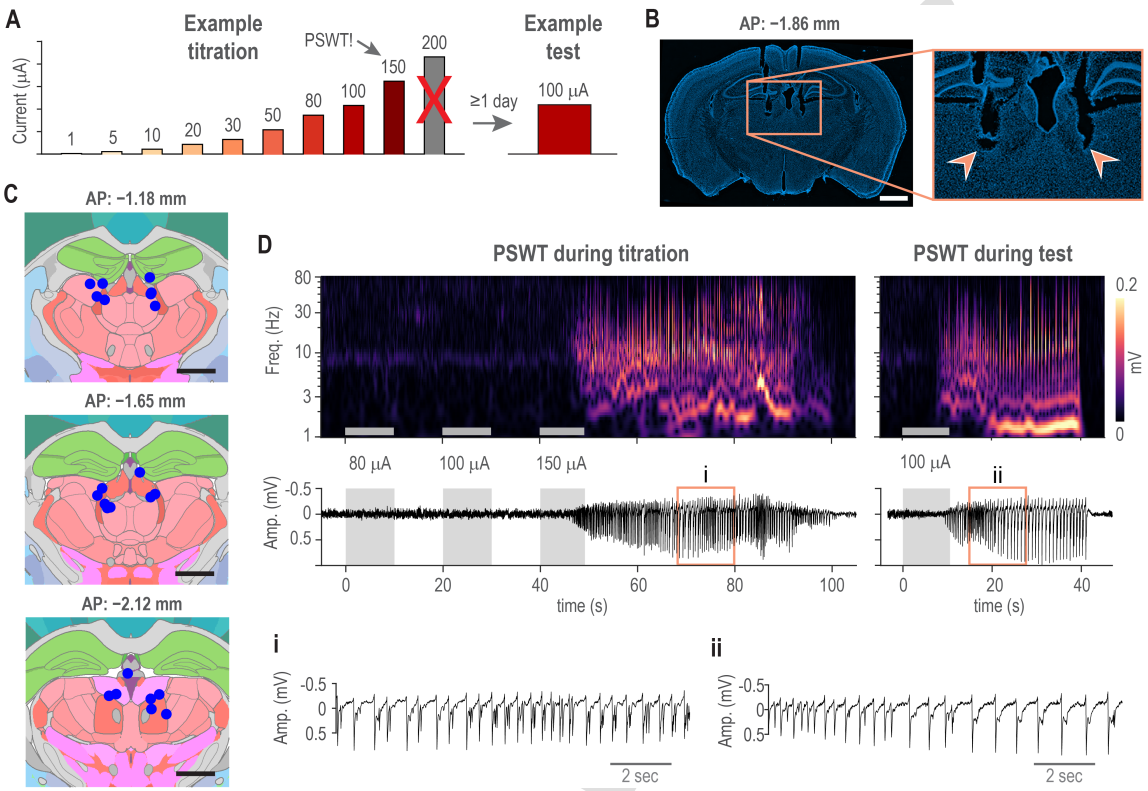

Figure 1: **Methods and example PSWTs induced by CT-DBS**. A) Schematic of an example titration-test protocol at a given frequency. During titrations, 10-s stimulations at the currents shown were performed until a PSWT was observed or 200 μA was reached. For example, if a PSWT occurred at 150 μA, the titration was halted, and the subsequent 60-s test was performed at 100 μA. B) Representative example of a DAPI-stained coronal slice at AP -1.86 mm from bregma with zoomed-in view of the electrolytic lesions, indicated with arrowheads. C) Summary of all electrode tip locations (blue dots) projected onto the closest of three coronal planes, AP -1.18, -1.65, and -2.12 mm. D) Example of a titration-test pair at 200 Hz. The scalogram (top) and parietal EEG (bottom) show a PSWT beginning during titration stimulation at 150 μA (left panel) and a PSWT beginning during the subsequent test stimulation at 100 μA (right panel). Zoom-in of the PSWTs observed in the parietal EEG (orange box) during titration (i) and during test (ii).

Data Analysis

Scalograms were computed using the continuous wavelet transform (CWT) with an analytic morlet wavelet as implemented in MATLAB. All EEG recordings were independently reviewed by two researchers and PSWTs present in at least one electrode were identified. Discrepancies were resolved by a third researcher. Summary statistics were computed as median and median absolute deviation (MAD). Analysis of PSWT features was performed using a generalized linear mixed-effects model [21] as implemented in the `lme4` R package [22], with PSWT duration, latency, or probability as responses; mice as random intercepts; and sex, laterality, stimulation frequency, and stimulation current as predictors. A normal distribution was used to model duration, gamma to model latency, and binomial to estimate probability. In all models, frequency and current were $\log_{10}$-transformed. The effect of previous PSWTs (within-day and across-day) was assessed but were excluded from final models based on a process of model selection using Akaike Information Criteria (AIC) [23]. Because the rate of PSWT occurrence was near

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zero, confidence intervals for empirical probabilities were calculated using the Wilson score [24] rather than the typical Wald method.

Results

We implanted the stimulation electrodes aiming to cover the central thalamus along the anteroposterior axis. A representative DAPI-stained slice shows the tracks and electrolytic lesions of an electrode pair (Fig. 1B). The AP coordinates of the electrode tips ranged from -1.0 to -2.4, covering several central thalamic nuclei (Fig. 1C, blue circles). Representative examples of PSWTs occurring in a titration-test pair are shown in figure 1D. PSWTs share similar characteristics with SWDs like the alternation between a fast (spike) and slow (wave) component, but often have multiple spikes preceding a wave. In this example, 150-μA stimulation during a titration induced a PSWT (Fig. 1D, left), but stimulation at 100 μA induced a PSWT in the subsequent test (Fig. 1D, right). Note the frequency modulation of the polyspikes between 1 and 5 Hz. It is unlikely our protocol leads to spontaneous PSWTs because out of 82 PSWTs, only one did not begin within 15 s after stimulation onset. This PSWT occurred 12.60 s after the offset of a previous PSWT and was excluded from further analysis. 96% of the PSWTs induced during experiments where both EEGs were recorded generalized to both hemispheres, and the three that did not lasted less than 2.2 s. The animals' behavior before and during PSWTs varied, but no tonic-clonic motor seizures were observed.

Considering that titrations were performed to find the highest current that would not cause a PSWT for each mouse, we anticipated that test stimulations performed at lower currents would not cause PSWTs. However, we found that 2.21% of test stimulations induced PSWTs (Fig. 2A), at currents between 20 and 200 μA. PSWTs were observed during test stimulations in 10 out of 12 mice (Fig. 2B, blue). However, estimation of individual probabilities is significantly higher than zero across the mice population (Fig. 2B, purple), which results in an overall significant probability of causing a PSWT during a test stimulation (2.21%, CI [1.46, 3.33]) (Fig. 2C, dashed line). Higher currents during tests had a higher probability of inducing a PSWT ($P = 1.97 \cdot 10^{-4}$, Fig. 2C).

We compared PSWT duration and latency to assess differences between PSWTs during both titration and test stimulations. Very short PSWTs (33%) which outlast stimulation by less than 2 s were excluded from further duration analysis (duration = 2.39 s, MAD = 0.99 s; Fig. 2D and Fig. 2E, open circles). The remaining 67% of PSWTs outlasted the stimulation by more than 5 s (duration = 30.21 s, MAD = 7.41 s). Regarding PSWT duration, there was no significant relationship with stimulation frequency ($t_{48} = 0.45$, $p = 0.66$, Fig. 2E, left), current ($t_{48} = 0.45$, $p = 0.65$, Fig. 2E, right), laterality of stimulation ($t_{48} = 0.52$, $p = 0.60$), sex ($t_{48} = -1.43$, $p = 0.16$), nor whether it was a titration or a test ($t_{48} = -1.14$, $p = 0.26$, Fig. 2E). Median latency from stimulation onset to PSWT onset was 5.63 s (MAD = 1.61 s). Stimulation frequency did not have an effect on PSWT latency ($t_{75} = 0.036$, $p = 0.97$, Fig. 2F, left), but current had a significant effect on PSWT latency ($t_{75} = 2.60$, $p = 0.011$, Fig. 2F, right), with shorter latencies at higher currents. There was also a significant difference in PSWT latency between test and titration ($t_{75} = 3.23$, $p = 0.002$, Fig. 2F), with shorter latencies associated with titrations. Sex and laterality of stimulation had no significant relationship to latency ($t_{75} = 1.33$, $p = 0.19$; $t_{75} = 1.17$, $p = 0.25$).

Discussion

We have shown that there is a small but significant probability that CT-DBS can induce PSWTs at stimulation currents as low as 20 μA. This occurred in 10 out of 12 mice, even after accounting for individual variability of PSWT-inducing currents through titration. The probability of inducing a PSWT during test stimulations increased with increasing current. We did not observe a significant difference in duration between PSWTs induced by titration and test stimulations nor was

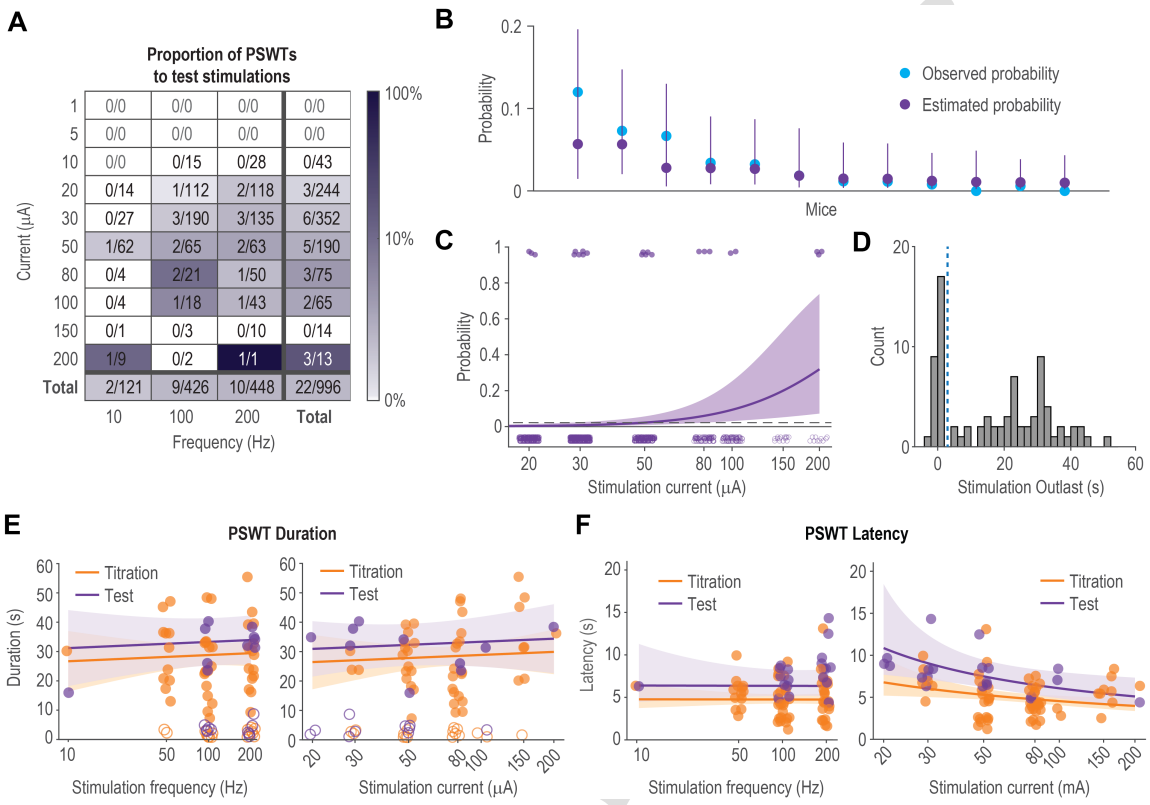

Figure 2: **Probability and features of PSWTs.** A) Frequency by current matrix with the number of PSWTs induced over the total number of stimulations performed. The percent of test stimulations that resulted in PSWTs is indicated by the color scale. Totals for each current are shown in the final column, and totals for each frequency in the final row. The bottom right cell shows the grand total PSWTs over the grand total of stimulations (2.21%). One stimulation (50 Hz at 200 μA) was excluded from the figure for simplicity but is included in the totals. B) Observed probability (blue dots), estimated probability (purple dots), and 95% CI (purple lines) of PSWT during test stimulations for each mouse. C) Total probability (purple line) and 95% CI (purple shade) of a PSWT occurring during test stimulations at different currents across all frequencies. The dots represent occurrence (upper) and absence (lower) of PSWTs across all test stimulations. Dashed line represents total probability of PSWT occurrence (2.21%). D) Histogram of the time each PSWT outlasted the stimulation. The dashed line shows the 2 s cutoff. E) The relationship between frequency (left) and current (right) and PSWT duration across titrations (orange) and tests (purple). F) Same as E but for PSWT latency.

there a relationship with stimulation current or frequency, likely because seizure stopping mechanisms are due to intrinsic homeostatic feedback [25] and are independent from stimulation parameters. PSWT latency was significantly shorter for PSWTs induced during titrations, likely due to the shorter off periods between titration stimulations leading to accumulation of extracellular potassium, which once elevated can take minutes to return to baseline [26]. Latency was also significantly shorter at higher currents, possibly due to a larger volume of effective stimulation recruiting more neurons [27]. We observed similar EEG characteristics in PSWTs induced by titration and test stimulations, probably due to intrinsic properties of thalamocortical circuits [28].

During wakefulness, CT-DBS causes electrographic seizures, like SWDs, in cats [11] and humans [14]. In NHPs it causes SWDs [12, 13] or behavior that resembles absence seizures [15].

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Electrographic seizures are not reported to occur during CT-DBS in humans in MCS [1, 2] nor anesthetized NHPs [3–5], possibly because lesions causing MCS result in low levels of neural activity. Similarly, most anesthetics suppress seizure activity. The frequency of spikes in the PSWTs we observed was typically modulated between 1 and 6 Hz, which is lower than the 5–7-Hz spikes seen in mouse models of absences epilepsy [29, 30]. It is also lower than, but overlaps with, the 2.5–5-Hz spikes typically seen in human absence seizures, where the median is around 3 Hz [31]. However, spikes during seizures induced by CT-DBS tend to have frequencies between 1 and 4 Hz [12, 14].

Awake CT-DBS causes electrographic seizures at different frequencies, currents (or voltages), pulse durations, stimulation durations, and lateralities. We tried both unilateral and bilateral stimulation at frequencies and a pulse duration consistent with previous reports [4], but we selected lower currents and shorter stimulation duration to diminish the chances of producing electrographic seizures or tissue damage [18]. While DBS may have both local and distant effects through stimulation of fibers passing near the electrode [27], optogenetic stimulation of the central thalamus produces electrographic and convulsive seizures in rats [17], suggesting that CT-DBS-induced electrographic seizures are due to local thalamic stimulation rather than distant effects.

Our aim was to test modulation of brain states with CT-DBS, while avoiding inducing electrographic seizures. However, we found that currents lower than the titrated current could induce PSWTs and there was experiment-to-experiment variability in PSWT-inducing currents within mice. This variability may be explained because the effects of DBS depend on the ongoing neural activity immediately preceding the stimulation [32]. Kindling effects are unlikely because the history of previous stimulation within and across days did not affect the probability of inducing a PSWT. Thus, EEG should be closely monitored for electrographic seizures when performing CT-DBS, especially in awake subjects.

CRediT author statement

Francisco J. Flores: Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Isabella Dalla Betta:** Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **John Tauber:** Formal analysis, Writing – original draft, Writing – review & editing. **David R. Schreier:** Formal analysis, Writing – review & editing. **Emily P. Stephen:** Formal analysis, Writing – review & editing, Supervision. **Matthew A. Wilson:** Writing – review & editing, Supervision, Funding acquisition. **Emery N. Brown:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

E.N.B holds patents on anesthetic state monitoring and control. E.N.B. holds founding interest in PASCALL, a start-up developing physiological monitoring systems; receives royalties from intellectual property through Massachusetts General Hospital licensed to Masimo. The interests of E.N.B. were reviewed and are managed by Massachusetts General Hospital and Mass General Brigham in accordance with their conflict of interest policies.

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DECLARATION OF INTERESTS

Emery N. Brown holds patents on anesthetic state monitoring and control; holds founding interest in PASCALL, a start-up developing physiological monitoring systems; receives royalties from intellectual property through Massachusetts General Hospital licensed to Masimo. The interests of Emery N. Brown were reviewed and are managed by Massachusetts General Hospital and Mass General Brigham in accordance with their conflict of interest policies. The rest of the authors do not have any interest to report.

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