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On the neural basis of deep brain stimulation evoked resonant activity

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Abstract

Objective: Deep brain stimulation can be a remarkably effective treatment for Parkinson's disease and other conditions; however, an electrophysiological feedback signal is needed to improve surgical accuracy and for optimising therapy according to patient needs. Evoked responses may provide such a signal, although it is crucial to determine that recorded potentials are of neural origin and not a consequence of stimulation artefacts. Here, we use several *in vitro* and *in vivo* methods to establish the neural basis of resonant deep brain stimulation evoked activity.
Approach: Recordings were obtained from deep brain stimulation electrodes in saline, in feline brain regions not expected to produce resonant neural responses, and in fourteen subthalamic nuclei in people with Parkinson's disease following stimulation with 60μs per phase biphasic current pulses with different polarities.
Main results: Electrodes in saline did not exhibit stimulation artefacts beyond 1ms. Changing the pulse polarity reversed the stimulation artefact. Electrodes in feline brain elicited early latency activity (<5ms); however, the activity did not resemble a decaying oscillation. Electrodes in human subthalamic nuclei evoked resonant neural activity that was not reversed by changing the pulse polarity. The latency of resonant peaks from stimuli with opposing polarities differed by about the expected amount and were strongly correlated (ρ=0.998, p<0.001). Resonant peak amplitudes were also strongly correlated (ρ=0.945, p<0.001).
Significance: The absence of resonant activity in recordings from electrodes in saline and feline brain, in addition to findings that resonant activity occurs in the subthalamic nucleus but not neighbouring white matter regions, demonstrates that such activity is not an artefact of the stimulation and recording system. Furthermore, non-reversal of resonant activity with changing pulse polarity in human subthalamic nuclei indicates that it is independent from stimulation artefact. Thus, these methods provide strong evidence of the neural basis of deep brain stimulation evoked resonant activity.

Keywords: Deep brain stimulation, evoked potentials, evoked resonant neural activity, Parkinson's disease

1. Introduction

Deep brain stimulation (DBS) is an established treatment for Parkinson's disease and other movement disorders that is also being investigated for a rapidly expanding range of neurological and psychiatric conditions [1-4]. DBS involves surgically inserting electrode arrays into specific subcortical structures, typically the subthalamic nucleus (STN) or globus pallidus interna for Parkinson's disease, and using an implanted pulse generator to deliver chronic electrical stimulation that alleviates symptoms.

Although DBS can be a highly effective therapy, several technical challenges can lead to suboptimal patient outcomes, including the following. 1) The brain structures targeted are only millimetres in size and positioning errors during electrode implantation can reduce efficacy, cause side effects, and require further invasive neurosurgery to revise the placement [5-7]. 2) The mechanisms of action of DBS are inadequately understood, making it necessary to use clinical observations to heuristically determine beneficial stimulation parameters for each individual patient. As the parameter space is vast and clinical effects can be slow to emerge, this can be a difficult and time-consuming process that can result in poor outcomes [7, 8]. 3) DBS devices constantly apply stimulation using fixed parameters, whereas patient symptoms and therapeutic needs are continually fluctuating [9]. Thus, constant DBS can at times be insufficient, resulting in inadequate symptom alleviation, or excessive, which can cause side-effects and unnecessarily waste implant battery life [10, 11].

These challenges could be addressed using an electrophysiological feedback signal. A signal that is spatially specific to the neural target could be measured intraoperatively and used to guide electrode implantation to the most beneficial location. Furthermore, a signal that is reflective of patient symptomatic state could be used to objectively compare different stimulation parameter combinations and to automatically adjust therapy according to actual needs.

DBS evoked potentials may provide such a feedback signal. Multi-phasic cortical evoked potentials have been reported following DBS pulses applied to several neural targets, including the STN, the globus pallidus, and the thalamus [12-18]. These responses have been found to vary with electrode position relative to the target structure and with stimulation parameters, suggesting potential utility as feedback signals. However, recording cortical evoked potentials intraoperatively introduces complexity into the surgical process and chronic monitoring would require additional electrode arrays implanted near the cortex.

A simpler approach is to record evoked potentials using the DBS electrodes themselves, which are already conveniently located within neural structures of interest. Short latency (<2ms) evoked compound action potentials (ECAPs) have been recorded from DBS electrodes in the thalamus and shown to vary with stimulation parameters [19, 20]. ECAPs have also been recorded from electrodes in the STN along with a peak several milliseconds later [21]. Furthermore, we recently reported an evoked response recordable from DBS electrodes in the STN that resembles a decaying oscillation lasting tens of milliseconds following each stimulus pulse, termed evoked resonant neural activity (ERNA) [22]. ERNA amplitude was found to vary across the STN, being greatest in the dorsal region where DBS is typically most effective for Parkinson's disease [23], indicating it could be a useful signal for guiding electrode implantation. ERNA morphology was also modulated across successive pulses, suggesting it may be useful for assessing the clinical effects of DBS and for adjusting therapy.

For an evoked potential to have clinical utility it is crucial to establish that it is of neural origin and not a specious artefact of the stimulation and recording system. This can be achieved using several *in vitro* and *in vivo* methods. Firstly, by applying stimulation to electrodes in saline, any contributions to the measurements from stimulation and recording artefacts can be determined in the absence of any neural activity [21, 24-26]. However, as saline does not completely reflect the recording conditions of an electrode in tissue, it is also informative to record responses from electrodes implanted in brain regions not expected to elicit the activity of interest. An additional method for distinguishing neural and artefactual activity is to apply stimulation pulses with alternate polarities [12, 13, 20, 25-27]. As anodic phase first (AF) and cathodic phase first (CF) symmetric biphasic pulses are predicted to produce comparable activation [28], the neural responses to both stimuli are expected to be similar. In contrast, the polarity of stimulation-related artefacts is expected to reverse across conditions, thereby distinguishing them from physiological responses.

Here, we use these methods to test the hypothesis that ERNA is of neural origin and not artefactual. Recordings were obtained from DBS electrodes in saline and in feline brain regions not expected to elicit ERNA in order to determine the contributions to the response from stimulation and recording artefacts. ERNA was also recorded from DBS electrodes implanted in 14 human STN using AF and CF stimulation in order to distinguish neural activity from stimulation-related artefacts.

2. Methods

Details specific to the saline, feline and human STN experiments are detailed separately below. All experiments used the same stimulation and recording equipment so that the results were directly comparable. This comprised a 16 channel DC-coupled biosignal amplifier (g.USBamp, g.tec medical engineering, Austria) and a highly configurable custom neurostimulator [29] (neuroBi, Bionics Institute, Australia). These devices were connected to DBS electrode arrays (model 3387, Medtronic, USA) via a relay box that connected all electrodes to the amplifier when not being used for stimulation.

The array comprised four ring electrodes (diameter: 1.27mm, length: 1.5mm) separated by 1.5mm. Additional silver/silver chloride electrodes were used as the amplifier reference and ground, and as the stimulation return. Electrodes used for stimulation were switched to the neurostimulator approximately 250µs before each pulse and back to the amplifier approximately 100µs after pulse completion. All non-stimulated electrodes remained connected to the amplifier during pulse delivery. All stimuli comprised symmetric biphasic pules (60µs phase width, 60µs interphase gap) delivered at 130Hz. A sampling rate of 38.4kHz was used and the amplifier included a 6.6kHz, 20dB/decade hardware-based anti-aliasing filter. No other filtering was applied to ensure that ERNA was not an inadvertent consequence of sharp cut-off filtering. In order to align measurements about zero, the baseline was removed from each recorded response by subtracting the median amplitude across 5-10ms; otherwise no signal processing was applied. Data processing and analysis was performed in MATLAB (MathWorks, USA).

2.1 Saline experiment

A DBS electrode array was submerged in 0.3% saline to approximate the conductivity of brain matter [30] (figure 1a). Two silver/silver chloride electrodes were also submerged for use as the amplifier reference/ground and stimulation return electrodes respectively. Stimulation was applied using the same paradigm previously used to measure ERNA in humans [22]. This involved applying bursts of 10 pulses (e.g. figure 1b), with one burst per second for 10 seconds. Burst stimulation was consecutively applied to each electrode of the array while signals were recorded from the unstimulated electrodes. Signals from electrodes delivering stimulation were not analysed due to long baseline recovery artefacts following each pulse that were not present in unstimulated electrode recordings. Stimulation was applied at 1.5, 3.38, and 7.59mA using both AF and CF pulses.

2.2 Preclinical experiment

With ethics approval (14_302AB) from the Royal Victorian Eye and Ear Hospital Animal Research and Ethics Committee and in accordance with the Australian Code of Practice for the Care and Use of Animals for scientific purposes and following the principles of the US National Institutes of Health guidelines regarding the care and use of animals for experimental procedures, a feline was implanted with a DBS electrode array. The animal was anaesthetised with xylazil (2mg/kg; subcutaneous) and ketamine (20mg/kg; intramuscular) and maintained with sodium pentobarbital (10 mg/kg; intravenous) to maintain end tidal CO_2 between 3-5% and respiration rate between 5-25 breaths/minute. A midline incision over the cranium was made to expose the dorsal surface of the skull, which was cleared and dried for fixation of a mounting post in

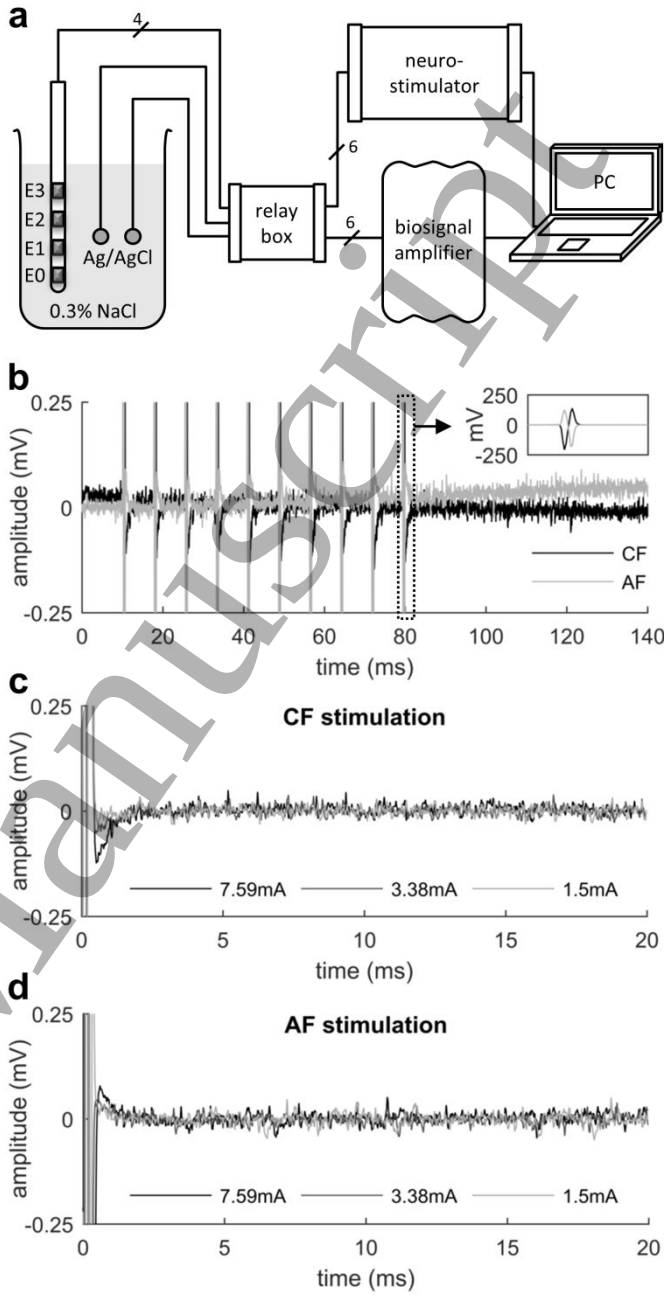

Figure 1 – Saline experiments. a) Experimental setup. b) Representative example of the stimulation artefacts caused by a burst of DBS pulses applied to electrodes in saline. Burst stimulation comprised ten 3.38mA pulses delivered at 130Hz using either anodic phase first (AF) or cathodic phase first (CF) symmetric biphasic pulses. Inset: Section of the recording inside the dashed box on a larger amplitude scale, illustrating the opposite polarity of AF and CF stimulation artefacts. c) Stimulation artefact following the last pulse (boxed pulse in b)) of the first burst for each CF stimulation condition. d) Stimulation artefact following the last pulse of the first burst for each AF stimulation condition. For recordings shown in b)-d), stimulated electrode: E2; recording electrode: E1.

the frontal sinus using stainless steel screws and dental acrylic. The DBS electrode was implanted through a small craniotomy targeted through the visual cortex towards the colliculi. The DBS electrode was positioned such that the topmost two electrodes were approximately within visual cortex and the bottom two electrodes were near the colliculi (figure 2a). Self-adhesive silver/silver chloride electrodes were placed on the animal's shaved back as the amplifier reference/ground and the stimulation return electrodes respectively, replicating the clinical setup. CF burst stimulation as described above was applied to each DBS electrode for 60s at 3.38mA. However, those stimuli were observed to occasionally cause minor twitching, possibly due to activation of the intercostal muscles by the stimulation return electrode on the back. As this was likely to introduce movement artefacts into the recordings, constant 130Hz stimulation – as typically used clinically to treat Parkinson's disease – was also applied. Stimulation was applied at currents between 0.67 and 7.59mA in 1.5x steps for 60s each. Due to 50Hz interference, recordings were re-referenced to bipolar combinations of the unstimulated electrodes for analysis. At the conclusion of the experiment, the animal was sacrificed with an overdose of anaesthetic sodium pentobarbital (150 mg/kg; intravenous).

2.3 *Clinical experiment*

Subjects were people with Parkinson's disease who were undergoing conventional DBS implantation surgery. Following ethics approval, subjects were recruited across Austin Hospital (SSA/15/Austin/266), St Vincent's Private (R0236-15), and Cabrini Hospital Malvern (02-15-02-16) in Melbourne, Australia. In accordance with the Declaration of Helsinki, informed consent was obtained from all subjects after the nature and possible consequences of the study were explained. The study was registered at www.anzctr.org.au (trial ACTRN12615001368527).

The clinical setup and surgical procedure were the same as those used previously [22]. As per the surgical team's standard clinical practice, 7 subjects were stereotactically implanted bilaterally with DBS electrode arrays, providing a total of 14 STN for testing. Electrodes were implanted along a trajectory determined from merged pre-operative magnetic resonance imaging and computed tomography scans aiming to position two electrodes in the STN and with the remaining electrodes above and below, respectively (figure 3a). After implantation, the DBS electrodes were temporarily connected to the experimental stimulation and recording equipment. Following the experiment, the electrode leads were internalised and connected to a clinical pulse generator (Activa, Medtronic, USA) implanted subclavicularly as per standard clinical practice. Self-adhesive silver/silver chloride electrodes placed on each subject's shoulders were used as the amplifier reference/ground and as the stimulation return electrode.

Experimental stimulation comprised monopolar burst

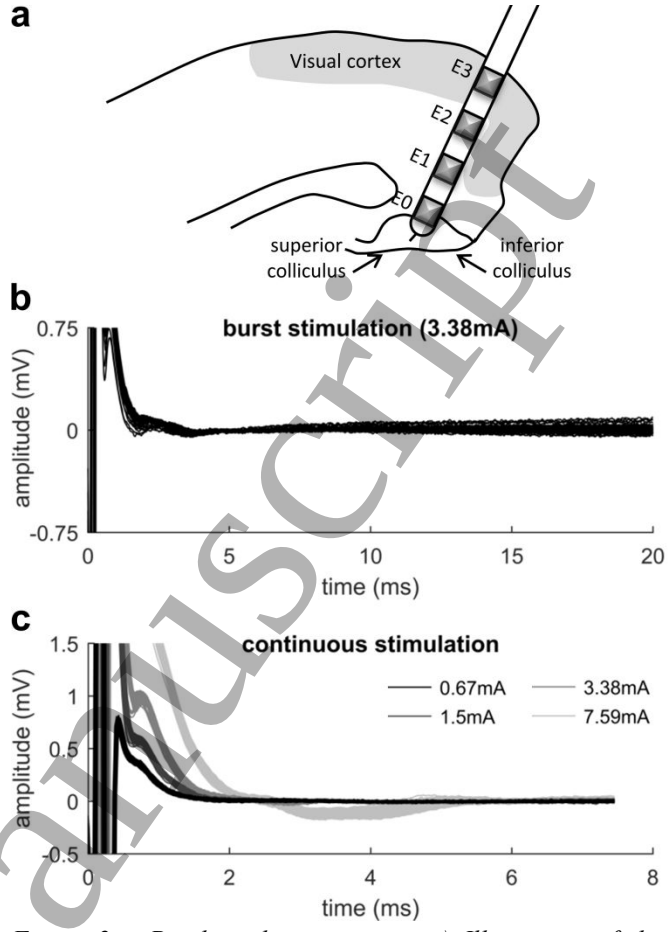

Figure 2 – Preclinical experiments. a) Illustration of the targeted electrode positions in a sagittal plane. b) Representative evoked potentials following the last pulse of each burst (60 responses shown). c) Evoked potentials occurring between continuous DBS pulses at 130Hz. The duration of responses is limited by the stimulation period (1/130Hz = 7.7ms). Responses shown are from all pulses in the first second after ramping up stimulation for the 0.67, 1.5, 3.38 and 7.59mA conditions (130 responses shown per condition). For b) and c), stimulated electrode: E1; recording configuration: E0-E2.

stimulation consecutively applied to each electrode as described above and reported previously [22]. Stimulation was applied at 3.38mA using both AF and CF pulses. Prior to analysis, recordings were re-referenced to an average of the electrodes implanted in the contralateral hemisphere to minimise 50Hz interference, e.g. $E0_{left} - {}^1/_4 \cdot (E0_{right} + E1_{right} + E2_{right} + E3_{right})$, $E1_{left} - {}^1/_4 \cdot (E0_{right} + E1_{right} + E2_{right} + E3_{right})$, etc.

To compare ERNA from AF and CF stimulation, the peaks and troughs occurring in each response were determined using the MATLAB 'findpeaks' function. ERNA peaks and troughs were defined as those that occurred in both the AF and CF recordings with a width between 0.5-2ms occurring within 2.5-20ms after the last pulse of each burst. Only peaks that were followed by a trough were analysed, to allow peak-to-peak

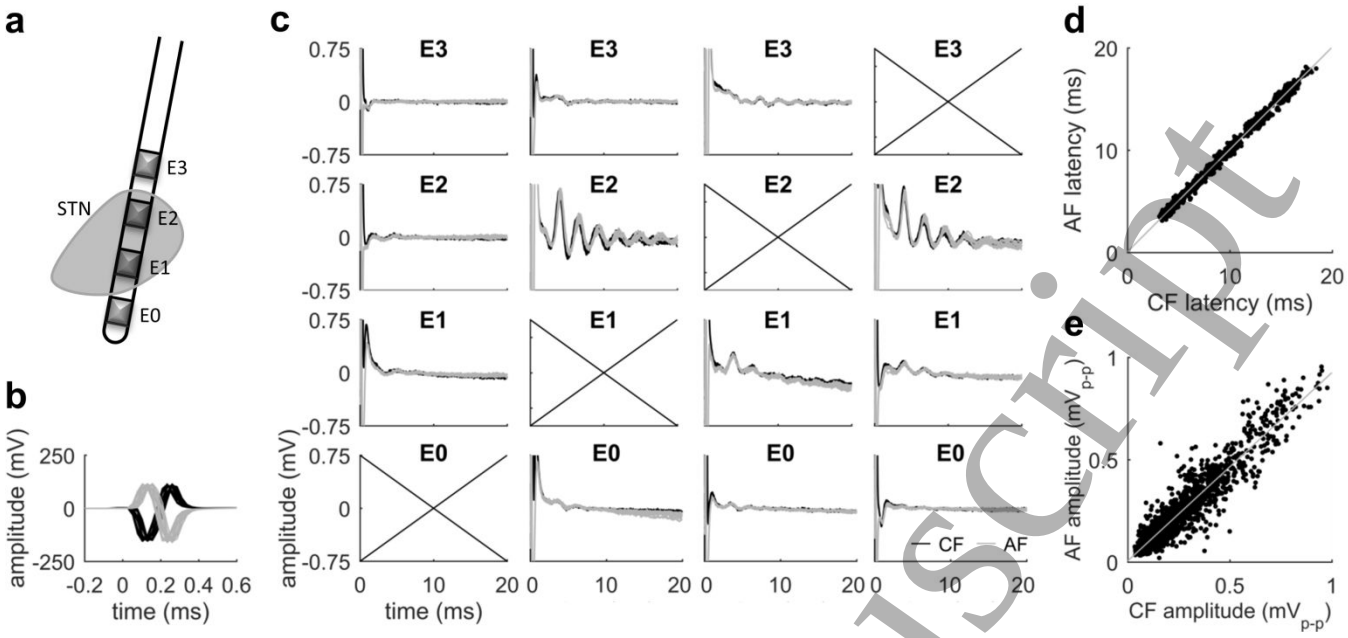

Figure 3 – Clinical experiments. a) Illustration of the targeted electrode positions with respect to the STN. b) Example of inverted stimulation artefact from AF and CF stimulation applied to the STN of a Parkinson's disease patient. Stimulated electrode: E1; recording electrode: E2. c) ERNA recorded from the same STN using AF and CF stimulation. Each column corresponds to a stimulation condition with the stimulated electrode indicated by the crossed axes. Responses shown are from the last pulse of each burst of stimulation (10 responses per condition). d) Latency of ERNA peaks for AF stimulation vs CF stimulation across all patients and electrodes. Grey line shows the linear regression. e) Amplitude of ERNA peaks for AF stimulation vs CF stimulation.

amplitudes to be calculated. Peaks were characterised by their latency relative to the onset of the first phase of each stimulus pulse and their peak-to-peak amplitude. Peak-to-peak amplitudes were used instead of absolute amplitude as 50Hz interference in some recordings added a variable baseline that falsely elevated or lowered peaks.

3. Results

Stimulation applied to electrodes in saline did not result in a discrete, measurable signal beyond the first millisecond after the pulse (e.g. figure 1b-d), even at very high currents. AF and CF stimulation produced stimulation artefacts with opposite polarity.

Stimulation applied to electrodes in feline brain regions not expected to elicit ERNA did not evoke responses with resonant morphology (figure 2b,c). Burst stimulation at 3.38mA produced activity within typically less than 5ms after each pulse, likely due to compound action potentials and stimulation artefacts (e.g. figure 2b). Increasing the current level of continuous stimulation amplified the early-latency activity and extended the baseline recovery time (e.g. figure 2c).

AF and CF stimulation applied to the STN of people with Parkinson's disease produced comparable ERNA (e.g. figure 3c), apart from minor differences within the first few milliseconds, likely due to the alternate polarity of the stimulus artefact. Across all STN and electrodes tested, a total of 2038 ERNA peaks were identified as occurring in both the AF and CF responses. The latency and amplitude of AF and CF ERNA peaks were strongly correlated (figure 3d,e; Pearson correlation, n=2038, latency: ρ=0.998, p<0.001; amplitude: ρ = 0.945, p<0.001). A linear regression of AF and CF peak latencies indicated that CF peaks occurred approximately 88µs before AF peaks. A linear regression of AF and CF peak amplitudes indicated that CF peaks were approximately 9% larger than AF peaks.

4. Discussion

This study used several *in vitro* and *in vivo* techniques to establish that DBS evoked resonant neural activity recorded from electrodes implanted in the vicinity of the STN are of neural origin and not specious artefacts of the stimulation and recording system. These findings support the potential clinical relevance of ERNA as an electrophysiological feedback signal for optimising therapy.

The lack of stimulation artefacts beyond 1ms in recordings obtained from electrodes in saline is indicative that the stimulation and recording system is not introducing prolonged artefacts that could underlie the resonant responses observed in human STN. This is supported by the measurements obtained from feline brain, which more accurately represents the electrophysiological conditions of DBS electrodes in neural tissue. While early latency activity (<5ms) activity was

observed, no activity was identified that resembled the decaying resonant morphology of ERNA, further indicating that the stimulation and recording system does not inherently produce resonant activity.

The saline and feline recordings also complement our previous report that ERNA does not occur in the posterior subthalamic area or the ventral intermediate nucleus of the thalamus of humans [22], two brain regions used to treat tremor disorders. The lack of ERNA in those regions is indicative that it is an electrophysiological phenomenon localisable to the STN, and not a ubiquitous response for DBS electrodes in human brain. This is further supported by the apparent variation in ERNA amplitude with electrode position relative to the STN, where electrodes targeted at the STN produce large-amplitude ERNA (e.g. E1 and E2 in figure 3c) and electrodes targeted outside the STN produce minimal or no ERNA (e.g. E0 and E3 in figure 3c). Thus, the absence of ERNA in recordings from DBS electrodes in saline, feline brain and other human deep brain regions under the same stimulation and recording conditions provides strong evidence that it is not artefactual but rather a response of the stimulated neural network localisable to the STN.

The non-reversal of ERNA with changing stimulus polarity provides further evidence that ERNA is of neural origin. Reversing the polarity of stimulus pulses is an established method for distinguishing neural activity from stimulation artefacts [12, 13, 20, 25-27]. If ERNA was an artefact of the stimulation and recording system it would be expected to reverse with changed stimulus polarity, as seen with the early latency artefacts in the saline recordings. However, the ERNA waveforms recorded in human STN were comparable for AF and CF stimulation, not reversed, implicating neural activity as the basis of ERNA. The earlier latency of CF peaks also emphasises the role of the cathodic phase of each stimulus pulse in generating ERNA. Previous modelling studies report that cathodic stimulation preferentially activates neuronal fibres over cells [28], suggesting fibre activation may predominantly underlie ERNA generation. The latency difference between CF and AF ERNA peaks (~88μs) is consistent with expectations given the known pulse timing.

In contrast to our previous report [22], in this study we deliberately did not apply any digital filtering or time-dependent detrending to the recorded responses to ensure that ERNA was not an inadvertent consequence of sharp cut-off filtering or other signal processing. The only filtering used was the 6.6kHz, 20dB/decade anti-aliasing filter of the biosignal amplifier. Based on figure 3c, in which approximately six peaks can be seen in a 20ms time window, ERNA frequency can be estimated to be around 300Hz. As the anti-aliasing filter cut-off frequency is considerably higher than the frequency of ERNA and the stimulation rate, ERNA is unlikely to be due to filter ringing artefacts.

Establishing the neural basis of DBS evoked potentials substantiates their clinical utility as a feedback signal. Previous research into electrophysiological feedback signals has predominantly focused on spontaneous local field potentials, recordable either from the DBS electrodes or from separate arrays in other brain regions [10, 11, 24, 31-33]. In particular, spontaneous beta-band (13-30Hz) activity has been associated with Parkinsonian bradykinesia and rigidity [34], used to establish the proof-of-concept of adaptive DBS [10, 35], and investigated as an intraoperative tool for guiding electrode implantation and for selecting stimulation configurations [36, 37]. However, due to their small amplitude, the use of such signals requires carefully designed amplifiers with large gain, low noise floor and effective stimulation-artefact rejection, which can be challenging to implement in fully-implantable devices [24, 38, 39]. Beta-band activity can also be temporarily abolished by micro-lesioning effects caused by electrode insertion, limiting its intraoperative use [36]. In contrast, ERNA has comparatively large amplitude and is not abolished by micro-lesioning effects, as evidenced by the distinct responses in figure 3c recorded immediately after electrode implantation. Thus, DBS evoked potentials such as ERNA have great promise as readily utilisable feedback signals for optimising DBS therapy to improve patient outcomes.

5. Conclusion

For an evoked potential to be clinically relevant and utilisable as an electrophysiological feedback signal for optimising DBS therapy it is vital to determine that it is of neural origin and not an artefact of the stimulation and recording system. Here, several *in vitro* and *in vivo* techniques have been used to establish the neural basis of resonant evoked activity recorded from DBS electrodes implanted in the vicinity of the STN.

The absence of resonant activity in responses obtained from electrodes in saline and feline brain demonstrates that such activity is not an artefactual product of the stimulation and recording system. Furthermore, non-reversal of resonant activity in human STN when the pulse polarity is changed indicates that it is independent from stimulation artefact. Thus, using these methods resonant neural activity evoked by deep brain stimulation has been shown to be of neural origin.

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