

Frequency dependent effects of deep brain stimulation: Clinical manifestations and neural network modelling

Zelma HT Kiss*, Dolen D Kirstein, Oksana Suchowersky, Bin Hu

Department of Clinical Neurosciences and Neuroscience Research Group, University of Calgary

Introduction

Electrical stimulation of deep brain structures has been performed since neurosurgeons began doing stereotactic surgery aimed at the thalamus and basal ganglia. Acute electrical stimulation was used to arrest tremor during brain mapping before burning a thalamotomy lesion. More recently this led to the use of chronic electrodes (deep brain stimulation, DBS) to treat movement disorders such as Parkinson's disease, essential tremor and dystonia. It is known that high frequencies (>100 Hz) are required to obtain beneficial effects on motor function [Benabid *et al.* 1996]. Anecdotal reports and one publication from 1960 [Hassler *et al.*] suggest that low frequency (5 Hz) electrical stimulation of thalamus can exacerbate tremor and more recently applied in the subthalamic nucleus can worsen akinesia [Moro *et al.* 2002]. The neural mechanism of this frequency-dependent phenomenon is unknown. The first aim of this study was to determine whether low-frequency electrical stimulation could worsen tremor amplitude in patients with thalamic DBS. The second aim was to explore the underlying neural mechanism through computer modelling.

Methods

Five patients with essential tremor, who had successful tremor suppression with thalamic DBS, underwent a frequency protocol while monitoring tremor with a triaxial accelerometer (EGAS-FS-25, Entran Devices Inc, NJ) on the contralateral hand, and surface EMG on forearm flexors and extensors (Bagnoli-8, Delsys, Boston). The frequency of stimulation applied was altered from 0-185 Hz and the stimulation intensity raised at each frequency to just sub-threshold for adverse effects, such as paraesthesia (numbness and tingling), speech disturbance, or muscle contraction. Tremor was monitored for 30-60 s while the limb was placed in an optimal position for eliciting tremor, most often holding a glass of water. Data was recorded on videotape after digitization using an 8 channel A-D converter (at 4.5 kHz/channel, VR-100B, Instrutech, NY).

Off-line, the data collected was replayed and digitized (CED 1401, Cambridge, UK). The 20-30 s of tremor data was divided into 5 s intervals and tremor amplitude for each time epoch determined using the root mean square (RMS) function (Spike 2, Cambridge, UK). For each patient, the RMS tremor amplitude was standardized by comparison to the tremor RMS amplitude at 0 Hz and reported as the percentage of tremor amplitude at 0 Hz. Also the power spectrum of tremor at each frequency of DBS applied was graphed. A fast fourier transform (FFT: 128 bins) was examined between 1-15 Hz to determine the dominant frequencies of the resulting tremor. Statistical analyses included non-parametric ANOVA (Friedman repeated measures) to compare the RMS amplitudes of tremor elicited at each DBS frequency applied (SigmaStat 2.03). All pairwise multiple comparisons were carried out using the Tukey method.

Computer modelling was performed using a three-layer neural network (Nodus). The middle layer of the network consisted of a pool of thalamocortical neurons, all of which exhibited rhythmic synaptic potentials mimicking tremor activity. A proportion of these cells were left subthreshold, while the rest were firing rhythmic action potentials. The convergent output of this thalamic activity was then relayed to motor cortex neurons via glutamatergic synapses with mixed AMPA and NMDA postsynaptic receptors. Based on our previous study in rat thalamic slices [Kiss *et al.* 2002], we mimicked the effects of DBS by introducing a sustained membrane depolarization to all the thalamic cells. The amplitude of this depolarization, as shown experimentally, is proportional to the frequency of DBS applied. The frequency and amplitude of the cortical response was then plotted against different frequencies of thalamic stimulation, assuming the cortical output reflects end-organ tremor activity.

Results

Root mean square tremor amplitude at each frequency of DBS applied is shown in Table 1. Tremor amplitudes were greater than baseline (0 Hz) at frequencies of 2 - 40 Hz and amplitudes were reduced at 75 Hz (ANOVA, $p < 0.001$). The most marked exacerbation was seen at an applied DBS frequency of 20 Hz (ANOVA, $p < 0.001$), resulting in a complete disruption of motor control of the arm in 4 patients. Even eliminating the outlier (patient 4) from statistical analysis, a significant increase in RMS amplitude at 20 Hz was identified. Whereas there was no significant difference in the peak frequency of tremor, at 10-40 Hz DBS there was a widening and increase in the power spectrum of the tremor recorded.

Table 1 RMS tremor amplitude shown as a % of tremor amplitude at 0 Hz (DBS off)

Patient	2 Hz	5 Hz	10 Hz	20 Hz	40 Hz	75 Hz	100 Hz	130 Hz	185 Hz
1	112%	94%	92%	225%	144%	53%	40%	38%	43%
2	39%	28%	29%	44%	67%	54%	43%	20%	23%
3	187%	261%	243%	275%	219%	4%	4%	4%	3%
4	183%	183%	149%	659%	36%	22%	20%	20%	21%
5	109%	217%	274%	324%	206%	87%	130%	95%	53%
mean	128%	156%	161%	309%	129%	48%	52%	34%	29%

To explore the underlying mechanism, we examined the possibility that the graded membrane depolarization we have demonstrated in thalamic tremor cells in the rat simulated DBS slice model [Kiss *et al.* 2002] can cause this phenomenon. In our neural network, we found that low frequency DBS and small membrane depolarizations (~5 mV) invariably enhanced the amplitude of rhythmic cortical output. Higher frequency DBS and larger membrane depolarizations started to evoke spontaneous thalamocortical firing unrelated to rhythmic synaptic input. Under this condition, the cortical output exhibited a DC shift; its output became smaller and less rhythmic. Further membrane depolarization from this level caused action potential inactivation (depolarization blockade) in thalamic cells, leading to an abolishment of rhythmic activities in both thalamus and cortex.

Discussion

Tremor can be worsened with low frequency thalamic DBS if the intensity of stimulation is increased above that chronically used to suppress tremor. Around 20 Hz DBS, in addition to a marked increase in amplitude of tremor, there was a widening in the tremor frequency spectrum.

Whereas neurosurgeons have anecdotally reported that low frequency stimulation can acutely exacerbate tremor [Hassler *et al.* 1960], this is the first report to quantify the changes in tremor resulting from different frequencies of electrical stimulation. Our previous attempts at worsening tremor with low frequency stimulation were unsuccessful because the intensity of stimulation was not increased above that required to suppress tremor chronically. One proposal to explain the tremor exacerbation is that the current applied spread further and affected more thalamocortical neurons. However, one would then expect a direct relationship between current applied and increase in tremor. This was not the case and the highest DBS current intensity applied occurred with the lowest frequencies (2, 5 Hz) and not with the 20 Hz DBS. The widening of the tremor power spectrum has been reported with high frequency stimulation although no mechanism has been proposed [Beuter *et al.* 2001].

These phenomena can be partially explained using a 3 layer network consisting of afferent inputs, thalamocortical and cortical output neurons. Small membrane depolarizations induced by DBS, enabled more thalamic neurons to fire action potentials at tremor frequency thereby recruiting more cortical motor neurons into the rhythmic firing pattern. Otherwise thalamic neurons had only subthreshold rhythmic synaptic potentials. An increase in the pool of motor neurons firing rhythmically would increase the amplitude of the motor output or movement. The increase in the complexity of the tremor may result from recruitment of more thalamocortical neurons firing at slightly different frequencies. DBS applied at high frequency range can abolish tremor through both its de-rhythmic effect and/or depolarization blockade in thalamic neurons. Finally, this study concerns mainly the short-term effects of DBS, on the scale of seconds to minutes. Long-lasting DBS in human thalamus may involve additional neural mechanisms that still require characterization.

References

- [1] Benabid AL, Pollak P, Gao DM *et al.* Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorder. *J.Neurosurg.* 1996; 84: 203-214.
- [2] Beuter A, Titcombe MS, Richer F, Gross CE, Geuhl D. Effect of deep brain stimulation on amplitude and frequency characteristics of rest tremor in Parkinson's disease. *Thalamus & Related Systems* 2001; 1: 203-211.
- [3] Hassler R, Riechert T, Mundinger F, Umbach W, Ganglberger JA. Physiological observations in stereotaxic operations in extrapyramidal motor disturbances. *Brain* 1960; 83: 337-350.
- [4] Kiss ZHT, Mooney D, Renaud L, Hu B. Neuronal response to local electrical stimulation in rat thalamus: Physiological implications for the mechanism of action of deep brain stimulation. *Neurosci.* 2002; 113: 137-143.
- [5] Moro E, Esselink RJ, Xie J, Hommel M, Benabid AL, Pollak P. The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology* 2002; 59: 706-713.