LETTER TO THE EDITOR

Deep brain stimulation in Parkinson's disease can mimic the 300 Hz subthalamic rhythm

G. Foffani1,2 and A. Priori1

1 Dipartimento di Scienze Neurologiche, Università di Milano, Fondazione IRCCS Ospedale Policlinico, Milano, Italy and 2 School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA, USA

Correspondence to: Prof. Alberto Priori, Dipartimento di Scienze Neurologiche, Clinica Neurologica, Padiglione Ponti, Ospedale Maggiore Policlinico, Via F. Sforza 35, Milano, 20122 Italy
E-mail: alberto.priori@unimi.it
doi:10.1093/brain/awl209


We read with much interest the paper by Meissner et al. (2005) recently published in Brain. The authors provided neurophysiological evidence that in MPTP-treated monkeys high-frequency (130 Hz) deep brain stimulation (DBS) of the subthalamic nucleus (STN) dramatically resets the firing activity of individual STN neurons, so that the firing probability is virtually zero immediately after each stimulus pulse and rapidly recovers to baseline levels before the appearance of the subsequent stimulus (significant firing rate increase within 4 ms). This DBS-induced resetting determines an overall decrease in the firing rate of STN neurons and disrupts abnormal oscillations at relatively low frequencies (<30 Hz). The authors 'focused on the 4–30 Hz range, since MPTP treatment induces almost exclusively significant oscillations in that frequency band'. They argue that the reduction of these oscillations could be at least partially responsible for the clinical benefits induced by DBS of the STN. Despite possible differences in the main frequencies of oscillations between human and non-human primates, the above interpretation is consistent with the dopamine-dependent reduction of beta oscillations observed in local field potentials (LFPs) recorded from the STN of patients with Parkinson's disease, as properly discussed by the authors, which were described in detail also by our group (Priori et al., 2004; Foffani et al., 2005, 2006; Marceglia et al., 2006).

LFP data from the STN of parkinsonian patients also suggest a more provocative interpretation of the results reported by Meissner et al. (2005). In a previous paper published in this journal, we found a fast rhythm operating in the human STN at surprisingly high frequencies, around 300 Hz (Foffani et al., 2003). The 300 Hz rhythm—which in our data set varied across nuclei between 230 Hz and 350 Hz—is boosted by dopaminergic medication and voluntary movement. In that paper we proposed that 'the clinical efficacy of DBS at frequencies >100 Hz could reflect its role as artificial (subharmonic) drive for the physiological neural oscillations at 300 Hz required for normal basal ganglia function. If we interpret the basal ganglia as a complex dynamic system, dopamine may be viewed as an external input that sets some internal variables at the working oscillatory equilibrium required for a correct output. When the dopaminergic system is defective as it is in Parkinson's disease, DBS would directly drive those internal variables into or closer to their physiological oscillatory equilibrium.' The results reported by Meissner et al. (2005) directly support our interpretation. In fact, they show that 130 Hz DBS (the 'external input') of the STN imposes a correlated oscillatory behaviour to the firing probability of STN neurons (the 'internal variables'), with a reset–recovery pattern that follows exactly the stimulation frequency ('closer to their physiological oscillatory equilibrium', i.e. subharmonically closer to the 300 Hz rhythm). In other words, DBS of the STN imposes a sort of lower harmonic of the 300 Hz rhythm to the firing probability of STN neurons, which is likely to pace the excitability of downstream neurons. Moreover, because DBS is likely to directly excite efferent axons (Hashimoto et al., 2003; Maurice et al., 2003; McIntyre et al., 2004), brain structures innervated by subthalamofugal projections will also receive the pacing of stimulus-locked axonal spikes immediately after each stimulus pulse, when the probability of firing of the soma is virtually zero (see above). Therefore, the net pacing effect of subthalamic DBS at 130 Hz on downstream neurons is most likely at twice the stimulation frequency, that is, at 260 Hz.

This prediction can be actually verified in a previous study by Hashimoto et al. (2003), who recorded the activity of neurons in the globus pallidus internus (Gpi) during DBS of the STN in MPTP-treated monkeys. They reported that DBS stimuli in STN induced two excitative responses in Gpi neurons separated by a latency difference of ~4 ms,
which corresponds to ~250 Hz and is within the range of the 300 Hz rhythm (Foffani et al., 2003). This latency difference appears as the highest peak in the inter-spike interval histogram of GPi neurons during high-frequency DBS of the STN (see Fig. 4B in Hashimoto et al., 2003), and corresponds exactly to the 4 ms latency between the supposed DBS-induced axonal spikes and the STN firing rate recovery reported by Meissner et al. (2005). The results by Hashimoto et al. (2003) and by Meissner et al. (2005) therefore nicely complement each other and together support our hypothesis that subthalamic DBS mimics the 300 Hz subthalamic rhythm by imposing neuronal synchronization in GPi at twice stimulation frequency (Fig. 1).

Our hypothesis would be further supported by evidence of LFP high-frequency synchronization occurring in STN during STN DBS. These experiments, however, would be technically challenging owing to the problems of artefact rejection. Nonetheless, according to our interpretation of the results reported by Meissner et al. (2005) and by Hashimoto et al. (2003), one would predict the LFP synchronization in STN to follow the stimulation frequency, whereas LFP synchronization should appear in GPi at double stimulation frequency. Moreover, the results reported by Meissner et al. (2005) suggest that the LFP high-frequency synchronization in STN should not last after turning DBS off, which is in agreement with our recent results (Foffani et al., 2006). It is important to remark that the exact elements generating the LFPs in the basal ganglia are not completely clear and that oscillatory LFP peaks do not necessarily reflect unitary oscillatory activity. There is increasing evidence, however, that LFP oscillations are correlated with single-unit activity, both in the beta band (Levy et al., 2002; Kühn et al., 2005) and in the gamma band (Trottenberg et al., 2006). Our hypothesis assumes that the correlation between LFP oscillations and single-unit activity extends to the 300 Hz rhythm, which should be experimentally verified.

Altogether, these observations suggest that subthalamic DBS could produce its clinical benefits not only by disrupting pathological oscillations at beta or lower frequencies (Brown et al., 2004; Meissner et al., 2005) but also by artificially mimicking the pacing action of the 300 Hz subthalamic rhythm, which is lost in Parkinson’s disease and could be critical for normal motor control (Foffani et al., 2003).

References


Letter to the Editor
