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High frequency stimulation of the subthalamic nucleus evokes striatal dopamine release in a large animal model of human DBS neurosurgery

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ABSTRACT

Subthalamic nucleus deep brain stimulation (STN DBS) ameliorates motor symptoms of Parkinson's disease, but the precise mechanism is still unknown. Here, using a large animal (pig) model of human STN DBS neurosurgery, we utilized fast-scan cyclic voltammetry in combination with a carbon-fiber microelectrode (CFM) implanted into the striatum to monitor dopamine release evoked by electrical stimulation at a human DBS electrode (Medtronic 3389) that was stereotactically implanted into the STN using MRI and electrophysiological guidance. STN electrical stimulation elicited a stimulus time-locked increase in striatal dopamine release that was both stimulus intensity- and frequency-dependent. Intensity-dependent (1–7 V) increases in evoked dopamine release exhibited a sigmoidal pattern attaining a plateau between 5 and 7 V of stimulation, while frequency-dependent dopamine release exhibited a linear increase from 60 to 120 Hz and attained a plateau thereafter (120–240 Hz). Unlike previous rodent models of STN DBS, optimal dopamine release in the striatum of the pig was obtained with stimulation frequencies that fell well within the therapeutically effective frequency range of human DBS (120–180 Hz). These results highlight the critical importance of utilizing a large animal model that more closely represents implanted DBS electrode configurations and human neuroanatomy to study neurotransmission evoked by STN DBS. Taken together, these results support a dopamine neuronal activation hypothesis suggesting that STN DBS evokes striatal dopamine release by stimulation of nigrostriatal dopaminergic neurons.

Deep brain stimulation (DBS) of the subthalamic nucleus is an effective treatment for Parkinson's disease (PD) [2,23]. Because the therapeutic effects of DBS are similar to those of a lesion [4], DBS has been thought to silence STN neurons [3,24]. As an alternative to a silencing mechanism of STN DBS, we have hypothesized that electrical stimulation of the STN activates surviving nigrostriatal dopaminergic neurons to evoke significant dopamine release in the striatum that, in part, contributes to therapeutic effects in PD patients [18–20,6]. Support for a dopamine neuronal activation hypothesis of STN DBS comes from both basic research and clinical observations. For example, Zhao et al. [33] have shown in MPTP hemiparkinsonian rhesus monkeys that chronic (tested up to 10 months) STN DBS results in significant striatal dopamine elevation as measured by microdialysis that corresponded to improvements in symptoms. In PD patients, bilateral STN DBS decreases or eliminates the need for L-DOPA [27,25], it is *most* effective in PD patients who respond well to L-DOPA [8], and is contraindicated for those who do not respond to L-DOPA [15], suggesting that therapeutic DBS requires endogenous dopamine production in the striatum. DBS may even elicit dyskinesias that resemble those seen when excess L-DOPA is given [23] and impulsivity, a dopamine-related behavior [12]. Together these experimental and clinical observations suggest the hypothesis that STN DBS may evoke dopamine release from surviving nigrostriatal dopaminergic neurons projecting to the striatum to contribute to its therapeutic effects, as well as elicit unwanted side effects when combined with inappropriately high doses of L-DOPA.

In this regard, using electrochemical techniques, including fast-scan cyclic voltammetry (FSCV), we have shown that high frequency stimulation (HFS) of the STN is capable of evoking striatal dopamine release in the intact rat [19,10]. In addition, we have also detected significant striatal dopamine release evoked by HFS of the STN in a well-recognized animal model of PD (dopamine nigrostriatal pathway lesions with 6-OHDA) [6]. Here, using a large animal

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(pig) model of human STN DBS neurosurgery, we applied FSCV in combination with a carbon-fiber microelectrode (CFM) stereotactically implanted into the striatum to monitor dopamine release evoked by a human DBS electrode unilaterally implanted into the STN. Several characteristics make the pig an excellent animal model to investigate STN DBS mechanisms in that it has face validity with human DBS surgery, and rivals that of DBS studies in non-human primate [32]. Adult pig brains (~160 g) are comparable in size to that of rhesus monkeys (~100 g) and baboons (~140 g), the volume of the pig STN ($50 \pm 7\ mm^3$) is comparable to that of the rhesus monkey ($34 \pm 6\ mm^3$) [14], and a pig brain atlas is available with significant similarities with human and non-human primates [11]. As such, we report here that the magnitude and temporal pattern of dopamine release evoked by STN electrical stimulation was both dependent upon stimulation frequency and intensity. Moreover, maximal dopamine release was obtained with stimulation parameters that are typically used with therapeutic DBS in PD patients.

The following experiments were performed in accordance with NIH guidelines (publication 86–23) and approved by the Mayo Clinic Institutional Animal Care and Use Committee. Four male pigs, weighing 26–30 kg, were initially sedated with Telazol (5 mg/kg i.m.) and xylazine (2 mg/kg i.m.), then intubated with endo-tracheal tube and ventilated with an artificial ventilator, then maintained with isoflurane (1%) for the remaining experimental procedure. In the prone position, the pig was placed in a MRI-compatible stereotactic head frame. A localizer box was then attached onto the head frame to create nine fiducials to enable localization of MR images in stereotactic space. For pre-operative targeting of the STN, MRI was performed with a General Electric Signa 3.0 T system. The DICOM image data were then transferred to a stereotactic planning computer and the anterior commissure – posterior commissure line identified on the MR images. Using COMPASS navigational software, MRI data was then merged with a pig atlas [11] and stereotactic coordinates for the DBS electrode implantation trajectory defined (Fig. 1A and B).

Thereafter, in the operating room a large midline incision of the skin was made to expose the cranial landmarks of bregma and lambda. This was followed by a burr hole made on the skull in line with our trajectory coordinates. A tungsten extracellular microelectrode (0.5–1.0 MΩ), mounted onto a microdrive, was then lowered using the same trajectory for the DBS electrode obtained by the navigation software to identify the final dorsoventral coordinates of the STN. Following electrophysiologic confirmation of the STN coordinates, a Medtronic 3389 human DBS electrode was then implanted into the STN target. The pig was then returned to the MRI scanner for post-operative confirmation of the placement of the DBS electrode (Fig. 1D).

For FSCV measurements, the recording CFM was prepared by aspirating a single carbon-fiber into a glass capillary, pulling to a fine taper on a pipette puller (Model PE-2, Narashige, Tokyo, Japan), and sealing with nonconducting epoxy [9]. Borosilicate capillaries containing the carbon fiber were pulled by a laser-based micropipette puller (P-2000, Sutter Instrument Co., Navato, CA). FSCV recordings of STN DBS evoked striatal dopamine release were performed using the wireless instantaneous neurotransmitter concentration system (WINCS), as per our previous published pro-

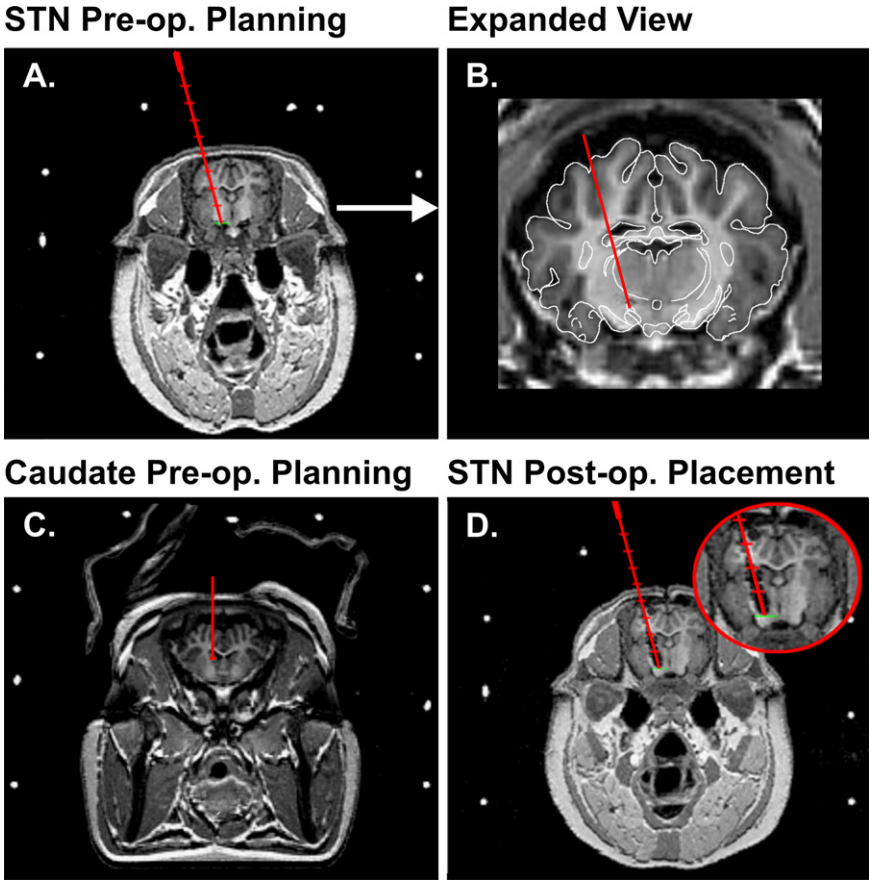

Fig. 1. (A) A representative coronal MRI and corresponding fiducials (white circles) on the MRI-compatible head frame for pre-operative planning and calculation of the trajectory coordinates (red line) for implantation of a DBS electrode in the STN of the pig. (B) Expanded view of the pre-operatively planned trajectory for implantation of a DBS electrode in the STN. (C) A representative coronal MRI for pre-operative planning and calculation of the trajectory coordinates (red line) for implantation of a carbon-fiber recording electrode in the caudate of the pig. (D) A coronal MRI showing the post-operative confirmation of the DBS electrode placement in the STN of the pig shown in (A).