

Dopamine Release in the Nonhuman Primate Caudate and Putamen Depends Upon Site of Stimulation in the Subthalamic Nucleus

Erika K Ross MS, PhD; Paul Hoon-Ki Min PhD; Hang Joon Jo PhD; Shinho Cho; Megan Settell; Ju Ho Jeong MD; Penny

Duffy PhD; Su-Youne Chang; Kevin Bennet MBA; Charles Blaha PhD; Kendall H. Lee MD, PhD

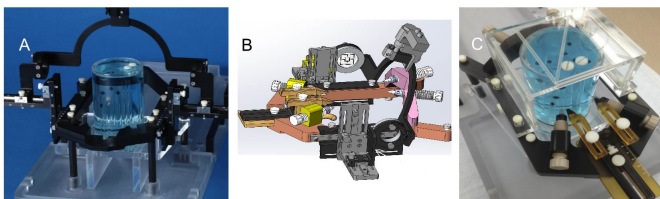
1. Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, 55905, USA 2. Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, 55905, USA 3. Department of Radiology, Mayo Clinic, Rochester, MN, 55905, USA *These authors contributed equally

Introduction

Electrical stimulation of deep structures of the brain, or deep brain stimulation (DBS), is used to modulate pathological brain activity. However, technological limitations and incomplete understanding of the therapeutic mechanisms of DBS prevent personalization of this therapy, may contribute to less than optimal outcomes. We have demonstrated that DBS coincides with changes in dopamine neurotransmitter release in the basal ganglia. Here we have mapped specific relationships between DBS and changes in neurochemical activity. Importantly, this study shows that DBS-evoked dopamine release can be minimized or maximized through subtle changes in the stimulation site.

Methods

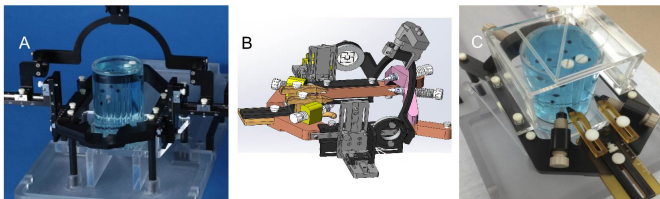
Stereotactic head frame



(A) MR safe Leksell frame for stereotactic surgery. (B) Head frame animation (C) Head frame with localizer box for image-based targeting.

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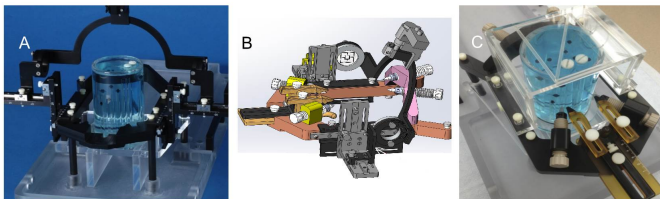
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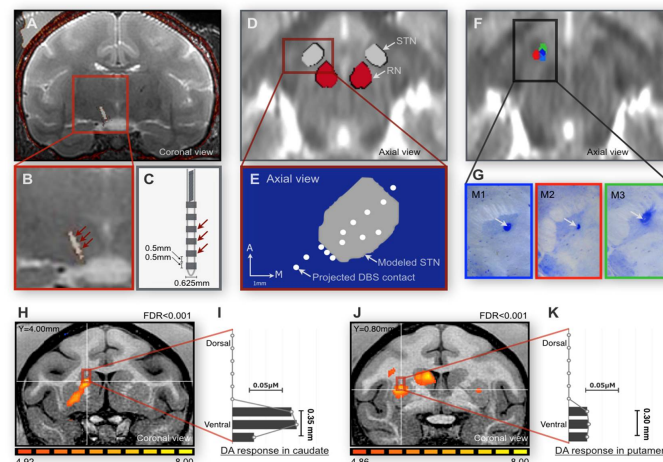
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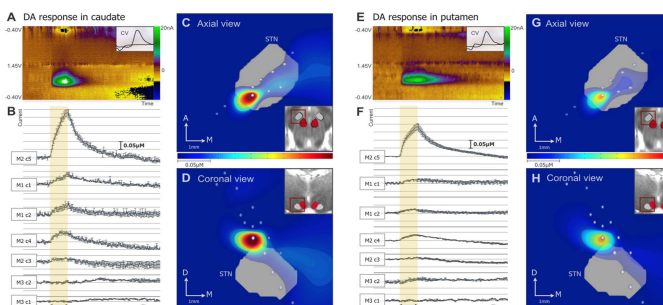


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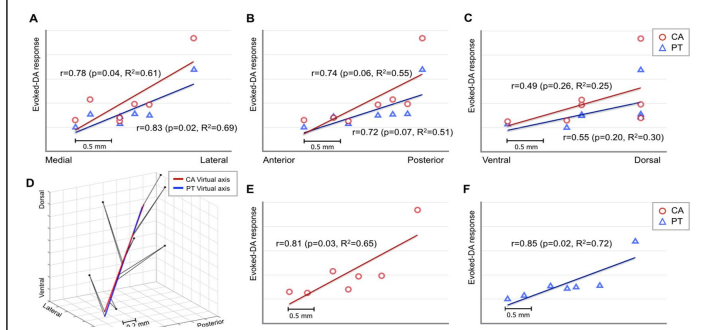
Results



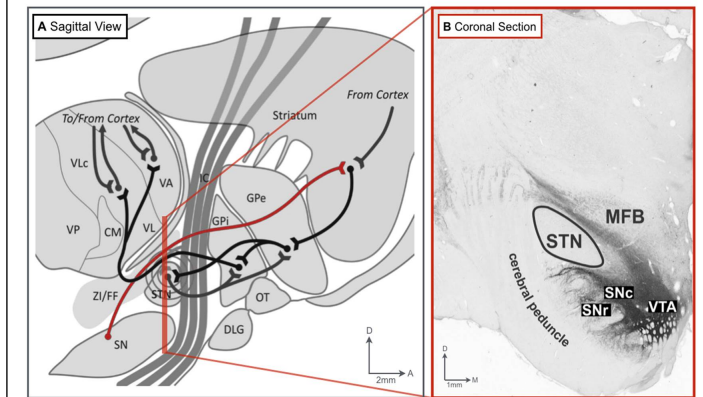
DBS and CFM targeting and confirmation. (A) within-subject MRI and CT fusion results showing the precise location of each DBS contact in the STN; (B) expanded view of the MRI-CT fusion image in a single subject showing the DBS electrode contact locations; (C) a schematic image of the multi-contact DBS electrode; (D) cross-modality registration for each subject's MRI-CT fusion image to a NHP brain template in which the location of STN is shown in gray and the RN in red during 3D co-registration using a normalized averaged T2 image from each subject (axial view); (E) a projection of all of the DBS contacts from each subject onto the 3D STN model in a representative axial slice; (F) the DBS contacts from each subject (indicated by red, green and blue) following normalization (axial view); (G) DBS contact location as confirmed by cresyl violet staining; (H and J) fMRI confirmation of the recording location in the caudate and putamen; (I and K) histograms of stimulation-evoked peak dopamine responses occurring selectively within regions of the caudate and putamen identified by maximum t-score BOLD voxel. Abbreviations: DBS (deep brain stimulation); CFM (carbon fiber microelectrode); STN (subthalamic nucleus); RN (red nucleus); BOLD (blood-oxygen-level-dependent).



DBS-evoked dopamine response map. (A) example of STN stimulation-evoked change in voltammetry DA response from caudate as shown in the representative pseudo-color plot; (B) mean±SEM DA oxidation current vs. time plot of stimulation-evoked dopamine release in the caudate and putamen relative to a single subject and a single contact as marked in the left panel (Average of n=3 data points); (C) axial view and (D) coronal view, showing STN stimulation-dependent differences in caudate DA release (n=51); (E) example of STN stimulation-evoked change in voltammetry DA response from putamen as shown in the representative pseudo-color plot; (F) mean±SEM DA oxidation current vs. time plot of stimulation-evoked DA release in the caudate and putamen relative to a single subject and a single contact as marked in the left panel (Average of n=3 data points); (G) axial view and (H) coronal view, depicting STN stimulation-dependent differences in putamen DA release (n=51). Abbreviations: DBS (deep brain stimulation); DA (dopamine); STN (subthalamic nucleus)



Directional relationship of STN stimulation site with evoked dopamine release in the CA (circles) and PT (triangles). (A) Relationship between electrode position in the STN (medial to lateral) and evoked DA release in CA and in the PT; (B) relationship between electrode position in the STN (anterior to posterior) evoked DA release in CA and the PT; (C) relationship between electrode position (ventral to dorsal) and evoked DA release in the CA and the PT. Abbreviations: Caudate (CA); Dopamine (DA); Putamen (PT).



Major anatomical pathways that are affected by STN stimulation. (A) diagram of the sagittal view of the location of the STN in relation to the medial forebrain bundle (red line) comprising the ascending dopaminergic nigrostriatal and mesocorticolimbic pathways. Diagram reprinted with permission from (Devergnas and Wichmann, 2011); (B) representative coronal section of tyrosine hydroxylase immunohistochemical analysis of dopaminergic projections in relation to the STN (Gale et al., 2013). Abbreviations: SNr (substantia nigra reticulata (dopamine dendrites); SNC (substantia nigra compacta) (dopamine cell bodies); VTA (ventral tegmental area).

References

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