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Evolving Characterization of the Human Hyperdirect Pathway

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Abstract

The hyperdirect pathway (HDP) represents the main glutamatergic input to the subthalamic nucleus (STN), through which the motor and prefrontal cerebral cortex can modulate basal ganglia activity. Further, direct activation of the motor HDP is thought to be an important component of therapeutic deep brain stimulation (DBS), mediating the disruption of pathological oscillations. Alternatively, unintended recruitment of the prefrontal HDP may partly explain some cognitive side-effects of DBS therapy. Previous work describing the HDP has focused on non-human primate (NHP) histological pathway tracings, diffusion-weighted MRI analysis of human white matter, and electrophysiology studies involving paired cortical recordings with DBS. However, none of these approaches alone yields a complete understanding of the complexities of the HDP. As such, we propose that generative modeling methods hold promise to bridge anatomy and physiology results, from both NHPs and humans, into a more detailed representation of the human HDP. Nonetheless, numerous features of the HDP remain to be experimentally described before model-based methods can simulate corticosubthalamic activity with a high degree of scientific detail. Therefore, the goals of this review are to examine the experimental evidence for HDP projections from across the primate neocortex and discuss new data which are required to improve the utility of anatomical and biophysical models of the human corticosubthalamic system.

Keywords

subthalamic nucleus; hyperdirect pathway; cortex

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Introduction

Direct cortical innervation of the subthalamic nucleus (STN), via the hyperdirect pathway (HDP), has been implicated in the modulation of a wide range of movement and decision-making behaviors [Aron et al., 2016; Frank, 2006; Nambu et al., 2002]. The HDP is also thought to play a role in several neurological disorders including, Parkinson's disease (PD), obsessive-compulsive disorder, and impulse control disorders [Nambu, 2005; Li et al., 2020; Dagher, 2020]. Imaging analyses and electrophysiological recordings have been performed in rodents, cats, macaques, and humans to support the presence of a layer V originating pathway, from wide-ranging cortical territories, onto the STN [see reviews, Mathai & Smith, 2011; Jahanshahi et al., 2015; Emmi et al., 2020]. As such, the acknowledged importance of the HDP in brain circuit function continues to expand. However, as new histological and electrophysiological results have become available, they highlight the need to better define the cellular characteristics of individual HDP neurons in greater detail (Figure 1).

Histological studies have defined the corticosubthalamic HDP in animals, but explicit anatomical confirmation of the HDP in humans is lacking. This represents a legitimate concern for human research studies that assume the existence of the HDP based on indirect techniques, such as tractography or electrophysiology. Considering the substantial differences between frontal and prefrontal cortical areas, as well as basal ganglia anatomy, between rats, monkeys, and humans [Mathai & Smith, 2011; Uylings & van Eden, 1991; Bakken et al., 2020], it is conceivable that the human HDP could be substantially different than what has been documented in experimental animals. For example, the human brain is ~14X larger, the primary motor cortex (M1) is ~8X larger, and the STN is ~7X larger in volume than those corresponding structures in the macaque [Hardman et al., 2002; Donahue et al., 2018]. In addition, white matter branching, geometry (e.g., myelination, fiber diameter), biophysics (e.g., excitability and conduction velocity), connectivity, and cortical projection topography can be substantially different between regions when comparing monkey to human [Firmin et al., 2014; Rilling et al., 2008; Schoenemann et al., 2005].

Biophysical modeling represent an established computational method to explain action potential generation and signal conduction of neurons in response to extracellular electrical stimuli [Rattay, 1999; McIntyre et al., 2004]. As such, biophysical models of HDP axons have been used to examine the neural response to subthalamic DBS [Gunalan et al., 2017] (Figure 2). However, most HDP models developed to date have been anatomically under-constrained [Bingham et al., 2021]. The anatomical details of the HDP axonal arbor in the subthalamic region can substantially influence the excitability of the HDP to DBS [Bower & McIntyre, 2020; Bingham & McIntyre, 2022]. Therefore, attempts to correlate HDP activation with electrophysiological [Howell et al., 2021] and/or behavioral measurements [Akram et al., 2017] are likely to be influenced by the accuracy of the patient-specific representation of the HDP in the model (Figure 2).

Attempts to define the HDP in humans are currently reliant on non-invasive imaging and interventional electrophysiological methods. These experimental approaches necessitate critical assumptions and simplifications on the anatomical details of HDP models [Petersen et al., 2019]. Ideally, complete post-mortem 3D reconstructions of human HDP cells

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would be used to constrain the construction of biophysical models of the human HDP, including mappings of their boutons and descriptions of patterns of myelination and cross-sectional geometry. However, lack of robust statistical distributions of these basic anatomical parameters reduces the opportunity for model-based representations to generate detailed predictions on the response of the HDP to stimulation [Gunalan & McIntyre, 2020]. As such, attempts to predict the effectiveness of neuromodulatory therapies, or to explain relationships between network dynamics and behavior, are limited and currently associated with relatively weak correlations [Horn et al., 2017; Howell et al., 2021].

New generative methods have been developed to enable the creation of populations of anatomically detailed HDP axonal morphologies which can be used in biophysical simulations [Bingham et al., 2021]. These new model-based techniques provide a promising approach to studying human white matter pathways which are incompletely described by empirical measurements [Bingham & McIntyre, 2022]. However, there exist many unanswered questions and unknown details about the HDP. Elucidating those details could improve scientific understanding of the HDP, and improve the predictive value of HDP models. Thus, the purpose of this review is to summarize current understanding about the anatomy and physiology of the monkey and human HDP and propose some directions for future research (Figure 2).

HDP Histology

Despite multiple negative reports of monosynaptic corticosubthalamic connections in NHPs [Levin, 1936, 1949; Verhaart & Kennard, 1940; Mettler, 1947; Carpenter, 1976], Nisino [1940], Petras [1969] and Künzle [1976; 1978] successfully described ipsilateral and somatotopically organized projections to the STN from cortex (Figure 3). Building on this work, Monakow [1978] demonstrated a lateral-medial and dorsal-ventral topography of cortical terminals within the STN, separating the M1 afferents from other frontal lobe inputs. These foundational anatomical studies were extended by Nambu et al. [1996], where they worked to more precisely clarify the topography of corticosubthalamic afferents. They electrophysiologically identified the primary motor cortex (M1) and the supplementary motor area (SMA) in NHPs. Then they employed targeted injections of horseradish peroxidase (WGA-HRP) and biotinylated dextran amine (BDA) to reveal a non-overlapping but reversed somatotopic map of motor afferent terminal topography within the STN. Nambu et al. [1996] found that M1 terminals were concentrated in the dorsal and lateral STN with the face, arm, and leg fields arranged contiguously. Near the end of the leg field, the SMA maps began in the central and medial STN. The SMA maps extended medially and ventrally, in reverse order: leg, arm, and face. They further defined the frontal eye field terminal topography as ventral within the medial half of the STN. Nambu et al. [1997] followed with additional tracings of the premotor cortical projections, where terminations were found to strongly overlap SMA but not M1 fields.

Early HDP investigations reinforced the concept of a “tripartite” parcellation for STN function [Parent & Hazrati, 1995], where the nucleus is hypothesized to be segregated into three functional territories that correspond to the motor, limbic, and associative circuits that course through the basal ganglia [Alexander & Crutcher, 1990]. However, the work of

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Haynes & Haber [2013] helped to revise basal ganglia anatomical models to more fully account for the overlap of terminal topographies within the STN. Revisiting the work of Monakow [1978], Haynes & Haber [2013] found that the non-motor cortices also strongly project to the STN. They used multiple anterograde/bidirectional fluorescent tracers injected into the ventral medial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), dorsal prefrontal cortex (dPFC), anterior cingulate cortex (ACC), M1, and SMA of NHPs (Figure 3). They found that vmPFC and OFC axons were concentrated on the medial tip of the STN, though likely targeting the lateral hypothalamus rather than the STN. dPFC terminals were found within the medial half of the STN. ACC terminals were sandwiched between dPFC and vmPFC/OFC fields, densely focused on the medial tip of the STN. Lastly, in rough agreement with Nambu et al. [1996], M1 and SMA afferents established dense terminal fields in the dorsal-lateral half and central STN regions, respectively. Notably, SMA exhibited a graded density from medial to lateral STN, where it overlapped with the M1 field.

While Haynes & Haber [2013] lacked the targeted injection approach sufficient to corroborate the precise somatotopy reported in Nambu et al. [1996, 1997], they established new topographies for non-motor afferents and forced the revision of anatomical models to account for strongly overlapping terminal fields from all HDP components [Alkemade et al., 2019; Jahanshahi et al., 2015; Wessel & Aron, 2017]. Moreover, when combined with knowledge of the STN neuronal topography, dendritic orientation, and morphometry [Sato et al., 2000; Bevan, 1997], it is likely that the overlap between fields is still underestimated. The dendrites of individual STN neurons likely extend over most of the STN in rats, but only ~1/5th in non-human primates and ~1/9th in humans, with most cells oriented parallel to the rostral-caudal axis of the nucleus and their principal plane parallel to that of the nucleus [Hammond & Yelnik, 1983; Yelnik & Percheron, 1979; Sato et al., 2000]. Thus, terminating afferents may be providing inputs to neurons with perikarya several hundred microns beyond the already extensive territories of HDP terminal topographies.

Coudé et al. [2018] took the step to define explicit 3D reconstructions of NHP hyperdirect axon collaterals in the subthalamic region. Following BDA injections into the upper limb region of the M1, layer V pyramidal neuron projections were traced into the internal capsule where they bifurcated toward the STN from the perinuclear capsular region (Figure 2). From there, the collaterals arborized with varying complexity throughout much of the lateral and central regions of the STN. M1 arbors yielded dozens to hundreds of primarily *en passant* boutons in the subthalamic region. Interestingly, none of the reconstructed HDP neurons that innervated the STN had collaterals to the striatum, suggesting a distinction between the corticostriatal and corticosubthalamic pathways in primates. Alternatively, a primate homology derived from data on the primary motor cortex of rodents would suggest ~9% of the HDP fibers should have collateralized to both the STN and striatum [Féger et al., 1994]. Nonetheless, it remains unclear whether other cortical regions contributing to the HDP are similarly distinct with respect to the striatum and STN. However, many of the primate HDP collaterals also projected to the zona incerta (~53%) and red nucleus (~21%) [Coude et al., 2018]. The corticofugal axon outer diameters in the internal capsule of the HDP axons were within the typical range for NHPs [Firmin et al., 2014, Kraskov et al., 2020]. However,

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with only 24 reconstructed neurons, it remains unclear whether HDP fibers collateralize discriminately from large, medium, or small myelinated fibers in the internal capsule.

NHP corticosubthalamic projections have also been studied at the level of the synapse in the STN. Mathai et al. [2015] confirmed in primates that motor-STN glutamatergic afferent synapses are primarily asymmetric and target STN dendritic shafts without a clear preference for small or large dendrites. Borgognon et al. [2020] has since extended this synaptic analysis to the premotor HDP as well. They showed that premotor HDP axons synapse more frequently with STN neurons than inputs from M1. However, Borgognon et al. [2020] did not find the clear degeneration of HDP synapses in MPTP parkinsonian monkeys that was previously observed in the M1-HDP [Mathai et al. 2015].

Lastly, we are aware of only a few modern-era histological studies of the human STN with relevance to the HDP. Alkemade et al. [2019] used immunoreactivity assays to highlight the topography of glutamate and GABA receptors in the human STN. They found a graded connectomic organization of the STN rather than clear parcellation of inputs, eschewing the tripartite parcellation of the STN. However, no method was used to differentiate between each of many potential glutamatergic input sources, leaving doubt as to how this result directly relates to respective components of the HDP. Nonetheless, the stereological analysis of Bokulić et al. [2021] found patchy collections of diverse cell types in the distribution of human STN neurons, which also led them to question the tripartite parcellation.

Non-Invasive Imaging

Ambitiously described as *in vivo histology*, MRI-based tractography has been enthusiastically employed to investigate cortical-basal ganglia connectivity in humans (Figure 4). Much of this work has focused on the STN as a region of interest (ROI) and employed various tracking methodologies, alongside broad cortical seed regions, to segment the STN into functional territories [Aravamuthan et al., 2007: Lambert et al., 2012; Brunenberg et al., 2012; Plantinga et al., 2018; Temiz et al., 2020; Neumann et al., 2018; Milardi et al., 2022] (Figure 5). Aravamuthan et al., [2007] examined scans from eight subjects, collected in a 1.5T magnet, where probabilistic tractography indicated connections between STN and dorsal premotor cortex, SMA, as well as hind, trunk, and forelimb M1. Largely in agreement with NHP work, premotor and SMA connections were more centrally located within the STN and topographically segregated from M1. Later, higher resolution diffusion weighted images ($1.7mm^3$) and somewhat more restricted connection criteria were used to reproduce a tripartite topography within the STN [Lambert et al., 2012]. Brunenberg et al. [2012] also reported tractographically identifying premotor, SMA, and M1 ‘hyperdirect’ streamlines in 7 of 10 subjects. Further probable connections were found, corroborated by fMRI correlation, from the orbitofrontal, dorsolateral prefrontal, superior and middle temporal, and parahippocampal cortices, as well as from fusiform gyri. In agreement with NHP tracing studies, a posterior lateral-medial gradient in motor connectivity and an anterior medial-lateral gradient in limbic connectivity was reported [Brunenberg et al., 2012].

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Plantinga et al. [2018] parcellated 7T datasets from 17 human subjects into motor, associative, and limbic cortical regions. Following tractographic analysis, each STN (subject & hemisphere) was segmented by connectivity and then statistically combined to yield a corticosubthalamic map of connectivity. Their results were generally consistent with NHP results, but the functionally segmented STN volumes varied widely across the 17 subjects. The motor regions ranged from 15% to 80%, associative from 12% to 88%, and limbic from 0% to 51% of the total STN volume [Plantinga et al., 2018]. To address questions as to whether there is associative cortical contribution to the HDP, Temiz et al. [2020] used tractography to suggest that STN afferents from associative cortical regions are less frequent than both motor and limbic regions. Another recent attempt was made by Milardi et al., [2022] to parcellate the STN into functional domains. This time four different tractography algorithms were tested against three cortical atlases. The estimated sensorimotor, limbic, and associative STN volumes proved highly sensitive to both atlas and algorithm choice. For example, the reported sensorimotor territory volume estimates ranged from 61 to 232mm^3. However, inter-subject variability was obscured by group normalization and thresholding. Unfortunately, in all of these human imaging-based studies, there is a lack of corroborating evidence from parallel histological or electrophysiological experiments. Therefore, a remaining challenge for tractography-based studies is to determine whether inter-subject variability is a natural feature of the corticosubthalamic system (or disease progression) versus methodological noise related to the limitations of diffusion-weighted imaging (DWI) data and the tractography algorithms (Figure 5).

In attempts to provide functional anatomical links to cognition, Coxen et al. [2012] paired DWI with a stop signal response task (SSRT) to correlate pre-SMA to STN connectivity with efficiency of response-inhibition. They showed that tract fractional anisotropy is predictive of task performance and linked pre-SMA-STN connectivity to age-related decline in response-inhibition efficiency. Mulder et al. [2014] further showed that vmPFC-STN probabilistic connections are a predictor of choice-bias performance. However, in agreement with NHP tracings [Lehman et al., 2011], vmPFC choice-bias involved streamlines perforate the striatum and course more ventral to internal capsule components known to collateralize to the STN, introducing doubt as to whether vmPFC contributes to the single-synapse corticosubthalamic pathway in humans [Mulder et al., 2014]. Indeed, fMRI studies of PD patients during subthalamic DBS demonstrate simultaneous activation of cingulate and insular cortex [Knight et al., 2015]. Further, positron emissions tomography studies showed activation in dlPFC, conflicted reports over ACC, and no increase in activity in OFC [Haegelen et al., 2005; Sestini, 2002]. However, the temporal resolution of these methods is too low to resolve multi-synaptic or common inputs-driven activity from direct activation of the HDP.

HDP Physiology

Behavioral and electrophysiological studies have also been used to support the presence of the HDP in humans. For example, Kuriakose et al. [2010] used scalp EEG in Parkinson's disease (PD) patients implanted with subthalamic deep brain stimulation (DBS) systems to demonstrate short (3 & 7 ms) and medium (14–22 ms) latency responses to DBS in the ipsilateral central frontal cortex. They concluded that the short latency EPs were too

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fast for multi-synaptic activity, which suggested direct HDP activation during DBS. Walker et al. [2012] further identified an even earlier signal (1 ms), presumably associated with antidromic activity in the HDP, in the human somatosensory cortex following subthalamic DBS. Postulating that relatively noisy EEG scalp recordings often include stimulus artifacts that obfuscate very short latency activity, Miocinovic et al. [2018] performed studies with intra-operative ECoG recordings. The electrodes were placed over motor and sensory cortex to demonstrate that subthalamic stimulation resulted in three distinct peaks of activity (2.8, 5.8, and 7.7 ms) which were strongest over M1, but also present over premotor and somatosensory cortex. The earliest peak (2.8 ms), was then correlated with clinically effective subthalamic DBS, suggesting that the therapeutic benefits of the stimulation are linked to activation of the HDP. More recently, simultaneous subthalamic DBS and ECoG have also been used to show rapid antidromic cortical invasion in inferior frontal and superior temporal gyri [Jorge et al., 2022].

HDP activity may be related to observed dopamine-sensitive oscillatory coherence between the STN and motor cortex in PD [Litvak et al., 2011; de Hemptine et al., 2015]. Therefore, the HDP is hypothesized to represent a therapeutic target for DBS, with the goal of disrupting pathological coherence. Johnson et al. [2020] examined this question at the single-unit level with recordings from M1 layer V pyramidal neurons in NHPs that were rendered parkinsonian and implanted with DBS systems. They documented the conditions under which fast antidromic activity occurred in M1 from either subthalamic or pallidal DBS. Several M1 units exhibited very short latency antidromic spiking, but ~50% of those cells showed a diminished firing rate over the first 50 seconds of high-frequency stimulation. These results suggested that cortical activation via recruitment of the HDP and/or internal capsule from DBS is either non-reliable or non-stationary.

Iwamuro et al. [2017] used cortical stimulation and systematic microelectrode recording in the NHP STN to map single-unit short-latency evoked responses. They found that STN cells responding to M1 and SMA stimulations were more medial and ventral than the respective topographic maps of terminating HDP fibers [Nambu et al., 1996; Haynes & Haber, 2013]. These results added electrophysiological support to the fuzzy functional parcellation hypothesis of the STN. Interestingly, no responding cells were seen in the dorsolateral quartile of the STN, where M1 terminals are the densest. This result was presumably due to the geometry and orientation of STN neuronal dendrites within the nucleus. Otherwise, only a small territory in the ventromedial STN was silent to motor cortical stimulation [Iwamuro et al., 2017].

By focusing instead on the frequency domain to indicate coupling strength, Herz et al. [2017] showed in PD patients implanted with subthalamic DBS that coupled oscillations between the STN (alpha band) and motor cortex (beta band) differentially adapted to either motor task speed (decreased coupling) or accuracy (increased coupling). Their results suggest that the motor HDP mediates this tradeoff, and current thinking is that the HDP facilitates the propagation of high beta frequencies from the cortex to the STN [Oswal et al., 2021]. It would then follow that subthalamic DBS leverages the HDP to manifest a bias toward speed over accuracy in motor behavior via the modulation of beta activity.

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Conflicting results can be found on whether subthalamic DBS improves [Santin et al., 2020; Gee et al., 2015] or exacerbates [Pote et al., 2016] impulsivity or impulse control behaviors. These kinds of differing results may relate to functional differences between the activation of motor or non-motor corticosubthalamic inputs, where the pre-frontal HDP is thought to actuate cognitive control over movement [Frank, 2006; Aron & Poldrack, 2006; Zavala et al., 2018]. It was, therefore, of interest when short latency EPs were recorded over the dorsal pre-frontal cortex in response to subthalamic DBS [Chen et al., 2020]. However, it is unclear whether DBS also caused internal capsule activation in addition to, or in lieu of, the purported short latency HDP activity [Bingham & McIntyre, 2022]. Nevertheless, DBS studies show that STN neurons throughout the dorsal and ventral half of the STN show decision preference in cognitive tasks [Al-Ozzi et al., 2020], adding behavioral evidence to the concept of functionally overlapping HDP maps in the STN.

Model-Based Insights

Until recently, the state of the art for creating human HDP biophysical models was direct application of axonal biophysics to streamline tractography or simplified pathway atlases [Gunalan et al., 2017; 2018; Howell et al., 2021; Gunalan & McIntyre, 2020]. While these efforts laid the groundwork for an improved understanding of HDP activation during DBS, their impact is limited by insufficient anatomical detail. Alternatively, Bingham et al. [2021] provides one example of an anatomically inspired HDP model that could be used to better understand the associations between electrophysiological recordings and behavioral measurements (Figure 6). After compiling detailed morphometrics from the Coudé et al. [2018] HDP axon reconstructions, and terminal topographies of the HDP from Haynes & Haber [2013], generative methods were used to create a population of anatomically realistic M1-HDP fibers. This HDP model was contextualized within a parcellated macaque brain atlas and presents a possible path forward to addressing limitations in tracing studies (sparsity) and tractography estimates (lack of anatomical detail). Later, Bingham & McIntyre [2022] presented a human HDP model that attempted to bridge both the species divide (macaque and human) and the imaging divide (histology and tractography) to create a population-level model of the M1-HDP. This approach allowed an exploration of the effects of detailed HDP terminal arborizations, and realistic mixed axon diameters, on the neural response to DBS. They simulated subthalamic DBS to predict HDP recruitment patterns under cathodal monopolar, anodal monopolar, and bipolar stimulation, as well as the spatiotemporal patterns of HDP APs arriving at layer V in M1 and throughout the STN (Figure 6).

The results of Bingham & McIntyre [2022] suggest that there is a fiber diameter and stimulus dependent distribution of conduction latencies and activation sites when analyzing DBS of the HDP (Figure 7). Large diameter HDP fibers are very easily activated in the internal capsule and conduct quickly to M1. As such, the large diameter HDP APs could contribute to very short latency EPs, but they are accompanied by, and likely dominated by, simultaneously activated fibers of passage in the internal capsule. However, when considering the activation of smaller diameter HDP axons, the signals arrive in cortex after the short-latency window (~3 ms) defined by Miocinovic et al. [2018] as being correlated with therapeutic benefit. Therefore, the specificity of ECoG for detecting and measuring

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HDP activity is not likely to be a clean as assumed by clinical experimentalists. However, thorough resolution of this concern requires better description of human HPD anatomy and physiology.

Biophysical models largely dispute assertions that antidromic conduction fails in the axonal arbor of HDP neurons following DBS-induced activation [Bingham & McIntyre, 2022; Anderson et al., 2018]. However, it is likely that the axosomatic regions of neurons perform a low pass filtering of antidromic action potentials invading the cell body at higher stimulating frequencies [Anderson et al., 2018; Yi & Grill, 2018]. This phenonmenon could help explain the unreliable antidromic spiking observed in the single-unit recordings of M1 layer V pyramidal neurons during DBS [Johnson et al., 2020]. In addition, models posit that high-frequency stimulation causes synaptic vesicle depletion in layer V pyramidal cortico-cortical collaterals [Farokhniaee & McIntyre, 2019]. These theoretical possibilities present interesting avenues for coupled experimental and model-based investigation of how subthalamic DBS influences layer V pyramidal and cortical network behavior. Where the prevailing hypotheses suggest that high frequency HDP activation leads to disruption of excessive cortico-STN oscillatory behavior [Litvak et al., 2011; Levy et al., 2002; Tinkhauser et al., 2018; Oswal et al., 2020], and/or the generation of an information lesion within the circuit [Grill et al., 2004].

Despite wide-ranging investigations on HDP activity, critical anatomical and physiological details of the pathway remain poorly characterized. We propose that until these details are rigorously described at the cellular and synaptic levels, the clinical and scientific impact of biophysical models of the HDP are likely to be limited. Therefore, we have assembled a collection of open questions for future investigation.

Open Questions

The review paper by Mathai & Smith [2011] posed more than a dozen important research questions on the HDP. Unfortunately, many of those questions remain largely unresolved despite years of active investigation from multiple research groups. Here, we have reframed a selection of those questions, and present some new ones, which we propose are particularly important for advancing our understanding of the HDP, and subsequently characterizing the neural response to subthalamic DBS (Figure 8).

(1) What is the trajectory, pattern of arborization, and morphometry of motor and non-motor HDP axons?

Coudé et al. [2018] described individual upper limb M1-HDP axons in detail, revealing STN, as well as zona incerta and red nucleus terminations. However, following the work of Borgognon et al. [2020], which highlighted varying boutons counts in the STN by projecting cortical region, it seems plausible that M1, SMA, pre-SMA, and prefrontal HDP axons not only have differing levels of connectivity to the STN, but also varying axonal geometries and arbors. In addition, both anatomical [Coudé et al., 2018] and electrophysiological [Pasquereau & Turner, 2011] results suggested that at the single cell level, the motor corticostriatal and corticosubthalamic projections are distinct. Therefore, we propose there

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is a need for more 3D histological reconstruction efforts focused on describing individual axons from the wide assortment of cortical regions that project to the STN.

(2) What is the degree of convergence of motor, associative, and limbic inputs onto STN neurons?

It remains to be shown that territorial segmentation of cortices projecting to the STN (i.e., tripartite parcellation) yields an analogous territorial mapping onto individual STN neurons. Terminal topographies based on broad cortical regions have been traced in monkeys [Nambu et al., 1996; 1997; Haynes & Haber, 2013], and tractography has indicated similar patterns in humans [e.g., Plantinga et al., 2018]. However, the mapping of corticosubthalamic terminals onto STN dendritic fields remains incomplete.

If there is a difference in the strength in convergence between premotor and motor corticosubthalamic projections, as measured as the number of boutons per terminal arbor [Borgognon et al., 2020], *(3) what is the true resolution of connectomic and morphometric variability within the HDP by cortical region?* Further, *(4) how does connectomic/morphometric mapping relate to rostral-caudal, medial-lateral, and dorsal-ventral maps?* The answers to these questions cannot be defined by HDP anatomical analyses alone, but also requires analysis of the dendritic anatomy and receptive fields of STN neurons.

(5) What are the biophysical properties of corticosubthalamic synapses?

Iwamuro et al. [2017] indicates that direct cortical inputs to the STN can strongly excite STN neurons, but the prospect of using population data to constrain individual synaptic models is daunting. Therefore, targeted tracings which resolve the relative numbers of axon terminals, coupled with experiments to assess the ability of HDP afferents to recruit STN neuron activity, are needed. One specific example would be the extension of Iwamuro et al. [2017] with methods which allow adequate spatial resolution to assess cell-level sensitivity and/or single-synapse analysis via glutamate uncaging [Adams & Tsien, 1993]. However, knowing the number of boutons per HDP arbor [Borgognon et al., 2020], the excitability of the STN by cortical region of input [Iwamuro et al., 2017], the relative strength of the synapses, and the terminal topography of anatomically distinct cortical inputs would greatly expand opportunities to dissect the biophysics of STN activity [Milosevic et al., 2021]. Therefore, multi-site cortical tracings and stimulation studies are needed to elucidate these details and to determine if the overlapping boundaries of STN parcellations are reflected in connective schemas at the cellular level.

Conclusions

The HDP has become an important focus of research because of its likely involvement in the mechanisms of subthalamic DBS. However, many anatomical and biophysical details of the HDP remain to be elucidated. While imaging and electrophysiology studies must drive progress toward understanding the HDP, each approach has weaknesses which hinder our ability to construct accurate biophysical models of the system (Figure 8). However, the creation of mechanistic biophysical models provides excellent opportunities for bridging experimental gaps, strengthening empirical conclusions, and understanding multi-scale

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dynamics of complex brain networks. This review provides our perspective on key open questions that should represent the focus of future scientific analyses on HDP anatomy and physiology. Answering these questions will enable development of the next generation of biophysical models. Such models promise to help drive definition of the next collection of open questions on HDP function.

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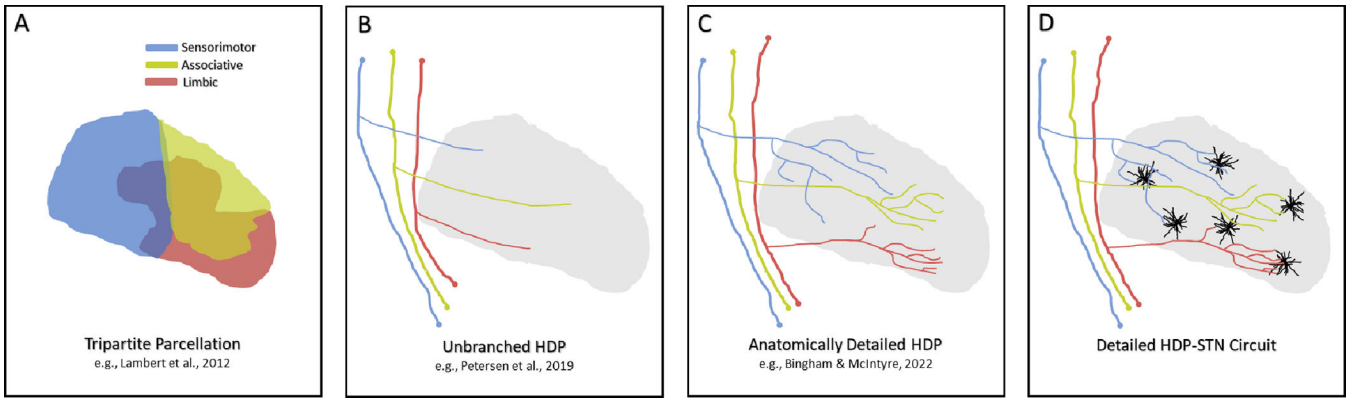

Figure 1.

Evolving description of the HDP. A) Tripartite parcellation of the STN based on white matter tractography [Lambert et al., 2012]. B) Simplified model of human HDP streamlines [Petersen et al., 2019]. C) Detailed generative models of HDP terminal branching [Bingham & McIntyre, 2022]. D) Explicit representation of synaptic innervation within the HDP-STN circuit.

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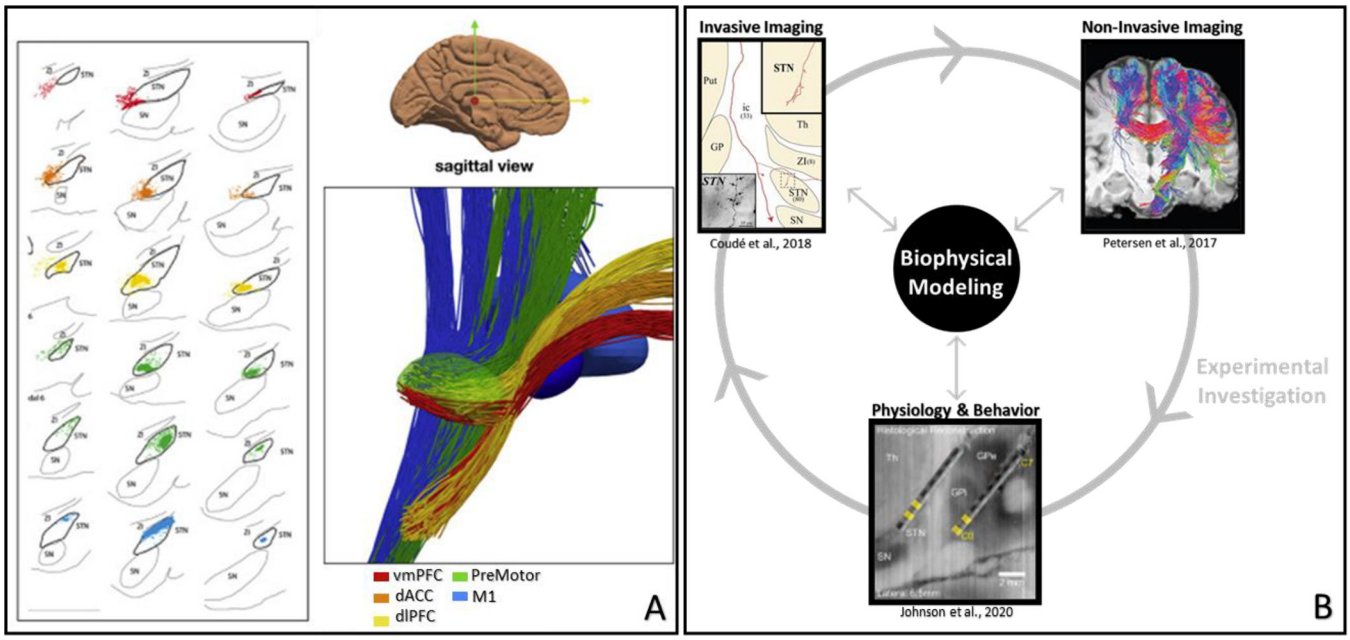

Figure 2.

Hyperdirect pathway. A) (Left panel) Non-human primate results from Haynes & Haber [2013] showing the terminal fields of HDP in the STN region. (Right panel) Human model of HDP streamlines from Petersen et al. [2019]. The cortical territory of origin is color-coded based on the common legend for both datasets. The green volume in the human model is the subthalamic nucleus and the blue volumes are the pallidum. B) Schematic of the conceptual interplay between experimental data and biophysical modeling to better understand the HDP.

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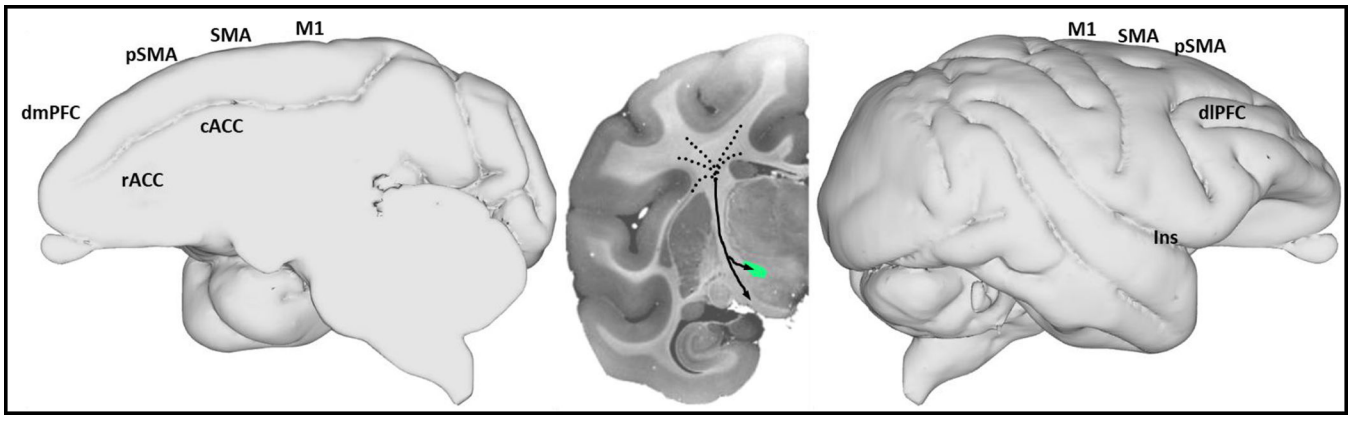

Figure 3.

Monkey HDP projections. Map of cortical projections (black lines) to the STN (green) based on NHP tracing studies. From left to right: medial, coronal, and lateral views of the macaque brain [Rohlfing et al., 2012]. Traced connections include the primary motor cortex (M1), supplemental motor area (SMA), pre-supplemental motor area and frontal eye fields (pSMA), dorsal and medial prefrontal cortex (dlPFC/dmPFC), anterior cingulate cortex (rACC/cACC), and insular cortex (Ins).

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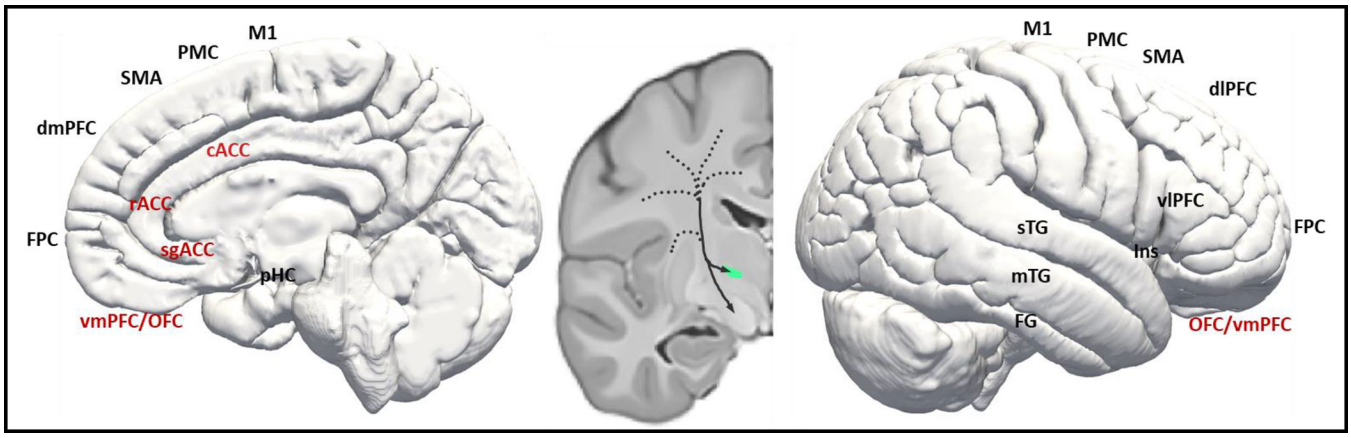

Figure 4.

Human HDP projections. Map of probable cortical-subthalamic (STN denoted in green) connections (black lines) based on human tractography. From left to right: medial, coronal, and lateral views of the CIT-168 human brain [Pauli et al.,2018]. Probable connections include primary motor cortex (M1), premotor cortex and supplementary motor area (PMC/SMA), dorsolateral prefrontal cortex (dlPFC), superior temporal gyrus (sTG), middle temporal gyrus (mTG), parahippocampal gyrus (pHC), fusiform gyrus (FG), medial frontal gyrus (MFG), anterior cingulate cortex (sgACC/rACC/cACC), inferior frontal gyrus and ventrolateral prefrontal cortex (vlPFC), ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), frontopolar cortex (FPC), and insular cortex (Ins). Red labels denote disputed or reduced-confidence connections.

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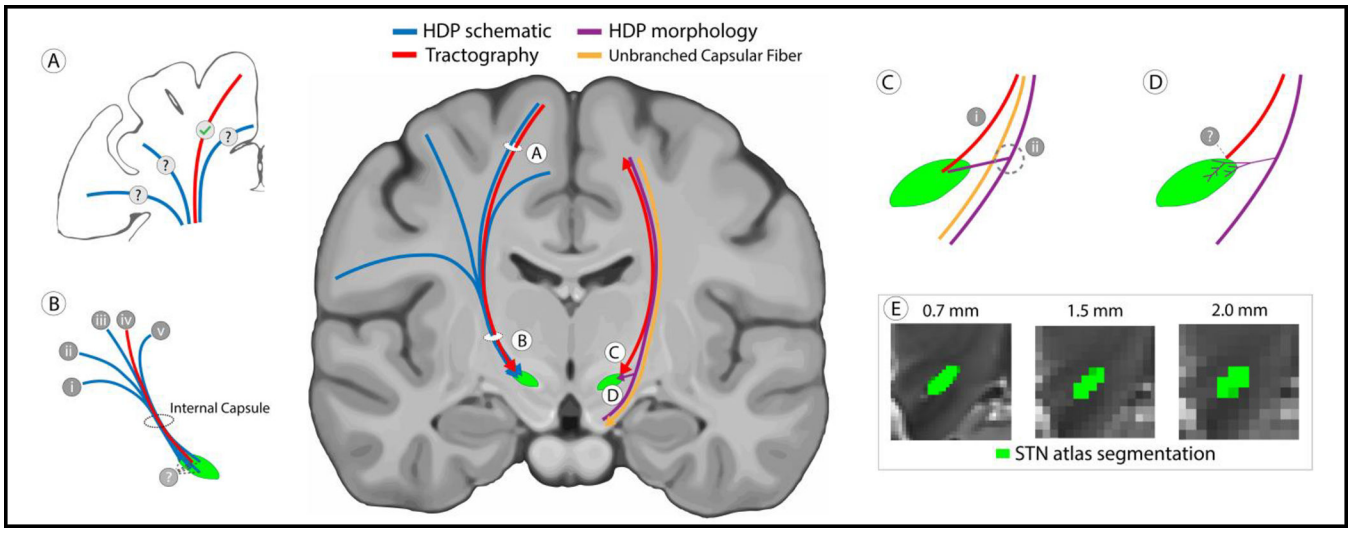

Figure 5.

Challenges of HDP tractography. A) Tractography often fails to reconstruct streamlines with a curved path (e.g., those to and from the lateral regions of the primary motor cortex). B) The "bottleneck effect" is problematic when attempting to track through white matter regions with a high degree of parallel pathway convergence, such as the internal capsule. C) HDP collaterals arise from long-range corticofugal axons passing between the cortex and brainstem. Tractography will not be able to accurately reconstruct collaterals from passing fiber bundles, especially should they be small, sparse, or unmyelinated. D) Tractography relies on a high degree of axonal organization in white matter regions (on a macroscale) and is not well-suited for modeling tortuous trajectories or axonal branching in grey matter regions. E) The validity of streamline termination within the STN is compromised by the definition of the nucleus in the image. The resolution of most DWI data (1.5 – 2.0mm isotropic), combined with the size (small) and shape (almond) of the subthalamic nucleus results in most voxels characterized as 'STN' being impacted by partial volume effects.

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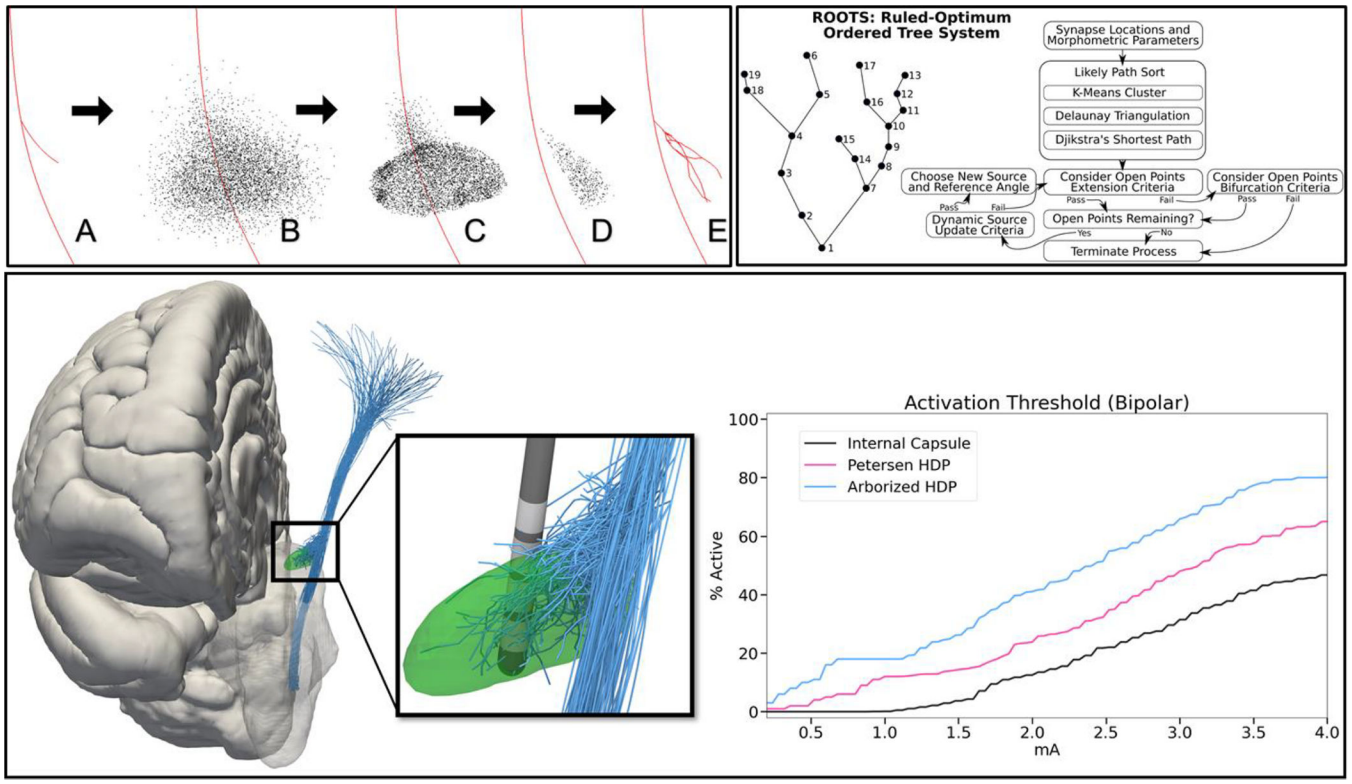

Figure 6.

Generative methods for axon modeling. (Top) Methods description a process for HDP generation. A) General anatomical prior for a HDP axon. B)Control points from the STN volume and anatomical prior axon collaterals are used to identify collateral branch points (C) control points are spatially resampled to bootstrap the volume arbors may target within the STN region, (D) a bifurcation point is randomly chosen and a cone filter was applied to the STN control points using the bifurcation point as a source and the STN motor region (dorsolateral) as a target, finally, (E) the ROOTS algorithm is then applied to the cone filtered control points with the bifurcation point as a source to generate new HDP terminal arbors. (Top Right) A visual example of the Ruled-Optimum Ordered Tree System (ROOTS) generating a constrained tree through a set of predefined control points. (Bottom) Activation threshold results from biophysical models generated via ROOTS. Simulations demonstrate the differences between simple and complex HDP representations. Adapted from multiple sources [Bingham et al., 2020; 2021; Bingham & McIntyre, 2022].

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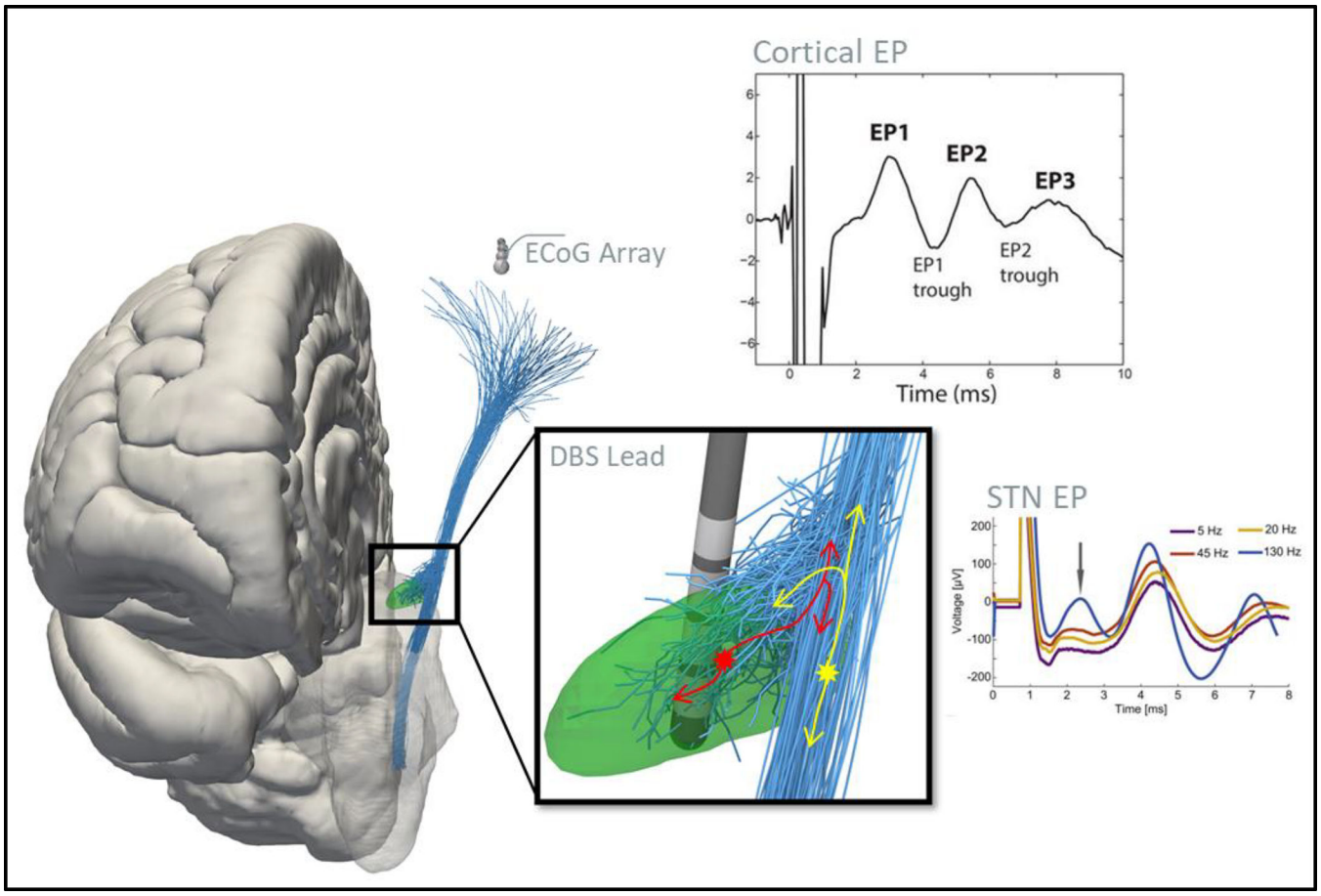

Figure 7.

DBS of the HDP. Biophysical models suggest that the site of action potential initiation in HDP neurons from DBS can be in either the subthalamic axon collateral or the corticofugal axon. Distinguishing recruitment order and patterns of action potential propagation (red star – initiation in the axon collateral; yellow star – initiation in the corticofugal axon) may help dissect the origins of cortical and STN evoked potentials (examples adapted from Miocinovic et al., 2018 and Schmidt et al., 2020), as well as providing insight into putative therapeutic roles of the HDP in subthalamic DBS.

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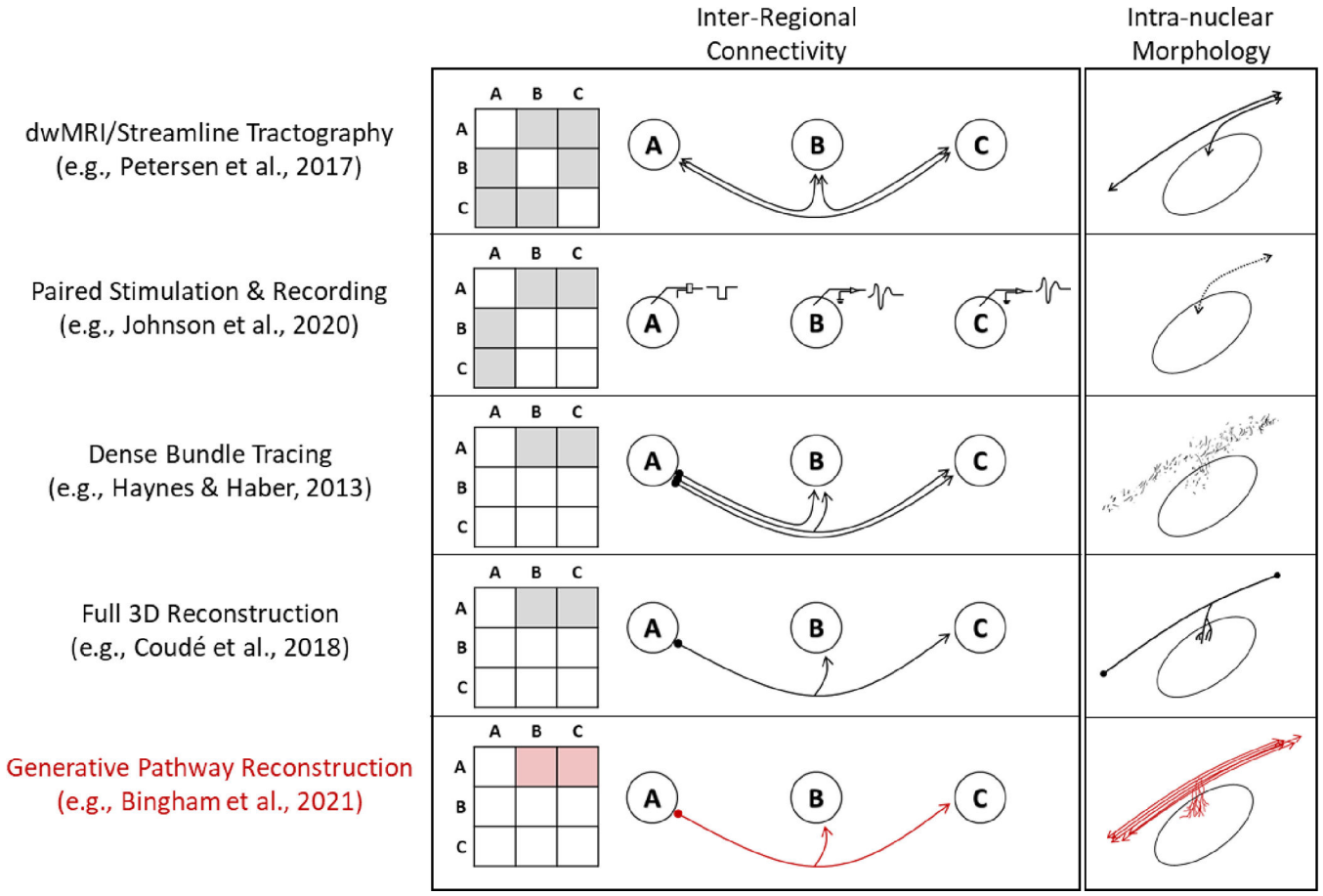

Figure 8.

Conceptual summary of methods for describing the HDP. Streamline tractography, without priors, yields un-directed inter-regional connections, but fails to capture most morphological details. Paired stimulation & recording is a highly flexible method which can confirm the presence of explicit connections between neurons or groups of neurons. However, electrophysiology, alone, provides no morphological information. Dense bundle tracing provides population-level anatomical information, though technical challenges prevent accurate description of individual axon morphologies. Despite the risk of under sampling, full 3D reconstruction remains the gold-standard for both confirming inter-regional connections and detailed description of neuronal morphometry. Generative pathway reconstruction combines insights from each respective method to improve anatomical realism in a population-level representation.