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Computational modeling of pedunclopontine nucleus deep brain stimulation

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Abstract

Objective—Deep brain stimulation (DBS) near the pedunclopontine nucleus (PPN) has been posited to improve medication-intractable gait and balance problems in patients with Parkinson's disease. However, clinical studies evaluating this DBS target have not demonstrated consistent therapeutic effects, with several studies reporting the emergence of paresthesia and oculomotor side effects. The spatial and pathway-specific extent to which brainstem regions are modulated during PPN-DBS is not well understood.

Approach—Here, we describe two computational models that estimate the direct effects of DBS in the PPN region for human and translational non-human primate (NHP) studies. The three-dimensional models were constructed from segmented histological images from each species, multi-compartment neuron models, and inhomogeneous finite element models of the voltage distribution in the brainstem during DBS.

Main Results—The computational models predicted that: 1) the majority of PPN neurons are activated with $-3V$ monopolar cathodic stimulation; 2) surgical targeting errors of as little as 1 mm in both species decrement activation selectivity; 3) specifically, monopolar stimulation in caudal, medial, or anterior PPN activates a significant proportion of the superior cerebellar peduncle (up to 60% in the human model and 90% in the NHP model at $-3V$); 4) monopolar stimulation in rostral, lateral, or anterior PPN activates a large percentage of medial lemniscus fibers (up to 33% in the human model and 40% in the NHP model at $-3V$); and, 5) the current clinical cylindrical electrode design is suboptimal for isolating the modulatory effects to PPN neurons.

Significance—We show that a DBS lead design with radially-segmented electrodes may yield improved functional outcome for PPN-DBS.

Keywords

Parkinson's disease; neuromodulation; gait; neuron model

Introduction

Deep brain stimulation (DBS) within the mesencephalic locomotor region (MLR) of brainstem, which includes the pedunclopontine nucleus (PPN), has been shown to alleviate

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akinesia and gait disturbances in parkinsonian non-human primates (Nandi *et al* 2008, Pahapill and Lozano 2000). However, DBS within this anatomical substrate in humans has produced inconsistent therapeutic results. Clinical outcomes have ranged from positive effects on most parkinsonian motor signs (Mazzone *et al* 2005, Plaha and Gill 2005, Stefani *et al* 2007), positive effects only on gait and likelihood of falling (Moro *et al* 2010, Wilcox *et al* 2010), or little to no consistent therapeutic benefit (Ferraye *et al* 2010). Several factors that may have contributed to such variability include incomplete activation of neuronal pathways within the PPN and modulation of fibers passing near the PPN that have confounding effects on parkinsonian motor signs when activated. Inconsistent results between experimental and clinical DBS studies may also have occurred because PPN morphologies are different between the human and non-human primate. A method for predicting how implantation trajectory, lead position, and stimulation settings affect neuronal pathways in and around the PPN and how these results differ between non-human primate models and humans will help to clarify previous clinical findings and inform future research.

The anatomical target underlying the observed therapeutic effects of DBS on parkinsonian gait has largely been posited from correlation analysis of electrode position and clinical outcome, inferring that the brain regions immediately adjacent to the active electrode(s) represent the primary regions that are modulated by DBS (Ferraye *et al* 2010, Mazzone *et al* 2005, Moro *et al* 2010, Plaha and Gill 2005, Stefani *et al* 2007, Wilcox *et al* 2010). There are two primary challenges with this indirect approach. First, there is a need to develop imaging sequences with enough contrast (Zrinzo *et al* 2011, Zrinzo *et al* 2008) and physiological markers with enough consistency (Insola *et al* 2012, Weinberger *et al* 2008) to define the amorphous boundaries of the PPN (Winn 2006). Second, the approach provides an imprecise estimate of the volume of tissue modulated by DBS and lacks the capacity to quantify the subtle changes in neurophysiology that can occur when adjusting stimulation amplitudes, frequencies, and pulse widths. Experimental DBS studies in non-human primates have demonstrated that small deviations in stimulation parameters can result in significantly different firing patterns and rates in neuronal populations downstream of the DBS target (Hashimoto *et al* 2003, Johnson *et al* 2009). Together, the uncertainty in position and volumetric effects of DBS have led to several controversies over putative targets for therapy (Mazzone *et al* 2007, Stefani *et al* 2007, Yelnik 2007) and mechanisms of side effects (Ferraye *et al* 2009, Jenkinson *et al* 2012) with PPN-DBS.

When considering the mechanisms of DBS, several studies have noted that fiber pathways can play an important role in accurately interpreting therapeutic outcomes (Johnson and McIntyre 2008, Johnson *et al* 2012, Miocinovic *et al* 2006, Xu *et al* 2011). There are several fiber pathways adjacent to PPN, which given their proximity may be unwantedly modulated during PPN-DBS. The superior cerebellar peduncle (SCP), also known as the brachium conjunctivum, runs medially around the PPN with axons stemming from cell bodies in the contralateral dentate nucleus and interposed nucleus of the cerebellum (Naidich and Duvernoy 2009, Nieuwenhuys *et al* 2008). SCP fibers are known to carry information to the motor cortex through the red nucleus and thalamus near the fourth ventricle (Perrini *et al* 2012). When the SCP is lesioned at the level of the PPN (i.e. rostral to the decussation), motor coordination deficits can result contralateral to the side of the lesion (Kojima *et al* 1997, Matsumura and Kojima 2001). Additionally, the medial lemniscus (ML), whose axons arise from cell bodies in the cuneate and gracile nuclei, is a fiber pathway that runs lateral to PPN (Perrini *et al* 2012). Stimulation of the ML is thought to induce sensory paresthesias (Ferraye *et al* 2010, Mazzone *et al* 2008, Weinberger *et al* 2008). There are several other fiber pathways that project near the PPN, including the lateral lemniscus (LL) carrying auditory signals from the cochlear nuclei to the inferior colliculus (Perrini *et al* 2012), the central tegmental tract carrying limbic and oculomotor information from the ipsilateral red

nucleus to the ipsilateral inferior olivary nucleus (Koeppen *et al* 1980, Nathan and Smith 1982), and the anterior spinocerebellar tract carrying proprioceptive information to the cerebellum from the posterior grey column of the ipsilateral and contralateral sides of the body to the cerebellum rostral to the trigeminal nerve (Perrini *et al* 2012). Given the close proximity of these fiber pathways to MLR nuclei, it is important to put activation of MLR nuclei in the context of potential activation of these fibers.

In this study, we have developed a computational modeling framework that includes anatomically and biophysically-realistic models of two classes of PPN neurons as well as SCP, ML, and LL fiber pathways. The models provided a unique opportunity to investigate three questions: (1) What pathways are activated when performing a monopolar review across all four DBS electrodes? (2) How sensitive are these results to location of the DBS lead within the MLR? (3) Can a lead design with segmented electrodes enable more selective modulation of the PPN in cases of misaligned DBS leads?

Materials and Methods

Anatomical surface reconstructions

Three-dimensional surface reconstructions of the PPN, ML, LL, and SCP borders were segmented from coronal plates in a non-human primate brain atlas (Paxinos *et al* 2009) (figure 1a) and from pseudo-horizontal plates in a human brain atlas (Paxinos 1995) (figure 1b). The reconstructions were created by tracing the anatomical boundary of each nucleus or fiber tract across multiple plates (0.45 mm and 0.5 mm spacing between plates for the non-human primate and human atlas, respectively) and lofting the 2D contours into 3D surfaces using a non-uniform rational B-spline imaging method (Rhinoceros, Seattle, WA).

Deep brain stimulation lead position

The DBS lead was introduced into the anatomical model along an oblique trajectory. In the non-human primate model, the lead was placed parallel to the fourth ventricle with an angle of 8° along the coronal plane and 25° along the sagittal plane such that the most distal electrode resided at or slightly below the caudal border of PPN (figure 1a,b). A similar trajectory paralleling the fourth ventricle was used in the human model, adjusting slightly for the altered anatomy of the PPN, with a lead angle of 14° along the coronal plane and 25° along the sagittal plane (Zrinzo *et al* 2008). These trajectories were similar to the trajectory described by Mazzone *et al.* (Mazzone *et al* 2008), who used 25° along the sagittal plane and 11-18° along the coronal plane, and Ferraye *et al.* (Ferraye *et al* 2010) whose planned trajectory was parallel to the floor of the fourth ventricle.

Three electrode geometries were investigated including a clinical DBS lead for the human model, a scaled-down clinical DBS lead for the non-human primate model (Elder *et al* 2005), and a radially-segmented DBS lead for the human model (Keane *et al* 2012, Martens *et al* 2011). A Medtronic 3387 lead (4 electrodes; 1.27 mm diameter; 1.5 mm height; 0.5 mm electrode spacing) was incorporated in the human model and a scaled-down version of the same lead (4 electrodes; 0.75 mm diameter; 0.5 mm height; 0.5 mm electrode spacing) was added to the non-human primate model. The radially-segmented DBS lead was designed to have greater than eight times the resolution of the standard human electrode. This design consisted of 16 rows, each containing four evenly distributed circular electrodes (0.7 mm diameter; 0.067 mm between rows).

Lemniscus and cerebellar peduncle axon models

Axonal tract morphologies were generated from histological contour reconstructions of ML, LL, and SCP. Each contour was randomly seeded with 400 points using a 'Jordan Curve'

algorithm, and each point in a given contour was connected with its ‘nearest neighbor’ point in an adjacent contour. Spline fits were then applied to the resulting sets of connected points across contours to generate three-dimensional traces for each axon in the population (figure 1c,d). In the NHP, the SCP tract coursed through the medial-caudal portion of PPN. Fibers that overlapped with the lead were removed from the model before simulation. In the NHP, LL and ML axons coursed along the lateral and anterior side of PPN, respectively, but did not overlap with any portion of the DBS lead. In the human model, no fibers coursed through PPN with ML coursing anteriorly, LL laterally, and SCP medially to PPN. None of the fibers in the human model overlapped with the DBS lead.

Axonal membrane dynamics were applied to each fiber and were consistent with previous studies (Johnson and McIntyre 2008, Johnson *et al* 2012, McIntyre *et al* 2004, McIntyre *et al* 2002, Miocinovic *et al* 2006). The 2 μm diameter myelinated axon model consisted of NODE (nodes of Ranvier), MYSA (myelin attachment segments), FLUT (paranode main segments), and STIN (internode segments) compartments connected to each other through an axial resistance. The nodes were modeled with fast Na^+ channels, persistent Na^+ channels, slow K^+ channels, and a leakage current responsible for nodal action potential. The paranode segments contained fast K^+ currents.

Pedunculopontine nucleus neuron distributions

The three-dimensional surfaces provided a boundary to populate reconstructions of PPN neurons including their axonal projections (figure 1e-h). Two primary types of neurons within PPN, cholinergic and glutamatergic, were populated within PPN according to a previous histological study (Lavoie and Parent 1994b). It should be noted that approximately 40% of cells in PPN are known to co-label for glutamate and acetylcholine, indicating that certain cells in the PPN may have dual effects on their downstream targets (Lavoie and Parent 1994a). These co-labeled cell types were not explicitly modeled in our study.

Type I neurons are considered non-cholinergic, while the majority of type II neurons are immunopositive for ChAT (choline acetyltransferase) (71%) (Takakusaki *et al* 1996). This distinguishing classifier was used to position the somas of each type of neuron in the PPN according to a previous histological study in non-human primates (Lavoie and Parent 1994b). Specifically, eight 40 μm thick slices were used to localize NADPH-diaphorase-labeled neurons (type I) and ChAT positive neurons (type II) within the PPN. Each position was extracted into our model and the slices were placed to match the constraints of PPN borders based on the brain atlas reconstructions. Soma positions for each cell type were distributed randomly in depth between slices. There was a generally consistent overlap between the brain atlas surface reconstructions of PPN and the borders of PPN defined by soma positions in the non-human primate histology.

PPN type I and type II neurons were reconstructed from camera lucida drawings (Takakusaki *et al* 1996) in Rhinoceros and were positioned in the PPN reconstruction such that the soma positions were consistent with the soma labeling distribution (Lavoie and Parent 1994b). Axonal efferents were oriented to project to atlas-based segmentations of thalamus, substantia nigra, brainstem, or spinal cord. A total of 1139 type I neurons and 1154 type II neurons were distributed within the context of the surface reconstruction of PPN. Other projections to the subthalamic nucleus (STN), globus pallidus internus (GPi), cerebral cortex, and striatum were not explicitly modeled, but could be inferred from the activation patterns identified in the modeled axonal projections stemming from PPN.

Pedunculopontine nucleus neuron morphologies

The two PPN neuron types were modeled in a multi-compartment framework in NEURON v7.2 (Hines and Carnevale 2009) with morphologies and electrophysiological characteristics consistent with previous studies (Kang and Kitai 1990, Lavoie and Parent 1994a, Lavoie and Parent 1994b, Takakusaki and Kitai 1997, Takakusaki *et al* 1996). Type I neurons consisted of an elongated cell body (31 μm long-axis, 13 μm short-axis, 20 μm thickness) with four primary dendrites (100-600 μm in length) and four axonal processes branching to the substantia nigra pars reticulata (SNr), thalamus, and spinal cord (Charara *et al* 1996, Lavoie and Parent 1994a) (figure 2a). Type II neurons consisted of a larger polymorphic cell body (50 μm long-axis, 24 μm short-axis, 20 μm thickness) with four primary dendrites (250-600 μm in length) and with four primary axonal processes projecting to the SNr, thalamus, and brainstem (Charara *et al* 1996, Lavoie and Parent 1994a) (figure 2b). Cells were oriented such that their axonal processes extended to their efferent targets (figure 2e). If a cell passed through the DBS lead or its encapsulation layer, that cell was labeled as damaged and deleted from the model. In the non-human primate model, this amounted to 456 type I (40%) and 537 type II (47%) cells labeled as damaged. Similarly, in the human model, 258 type I (23%) and 456 type II (40%) cells were considered damaged.

Pedunculopontine nucleus neuron membrane properties

Type I neurons, which have been characterized by low-threshold Ca^{2+} spikes without a transient outward current, were modeled with ion channels that generated an average firing rate of 10 Hz (figure 2c,d) (Jenkinson 2005, Takakusaki and Kitai 1997). Ionic currents in the soma and dendritic compartments of these type I neurons were defined according to the summation (figure 2a):

$$I_{ion} = I_{Na_f} + I_{Na_p} + I_{K_{DR}} + I_{Ca_T} \quad (1)$$

where each channel's current was written in the form of $I_{ion} = g_{ion} \eta (v - E_{ion})$ such that the maximum conductance g_{ion} was multiplied by one or more gating variables (η) that ranged from 0 to 1 (detailed in table 1).

$$\dot{\eta} = \alpha_{\eta} (1 - \eta) - \beta_{\eta} \eta = (\eta_{\infty} - \eta) / \tau_{\eta} \quad (2)$$

$$\eta_{\infty} = \alpha_{\eta} / (\alpha_{\eta} + \beta_{\eta}) \quad \tau_{\eta} = 1 / (\alpha_{\eta} + \beta_{\eta}) \quad (3)$$

Type II neurons, which have been characterized by a transient outward A-current without low-threshold Ca^{2+} spiking activity, were modeled with membrane properties consistent with (Takakusaki and Kitai 1997, Takakusaki *et al* 1996) (figure 2d). While a heterogeneous collection of cholinergic and noncholinergic type II cells have been identified in rodents, for the purposes of this study, we modeled only type IIa cells (Takakusaki and Kitai 1997, Takakusaki *et al* 1996). Dynamics of this cell type includes long-duration action potentials (2.3 ms), low-input resistance (123 Ω), a regular firing pattern, and a lower firing rate (8.5 Hz) exhibiting accommodation with depolarizing somatic current injection (Takakusaki *et al* 1997). Ionic currents in the soma and dendritic compartments of these type II neurons were defined according to the summation (figure 2b):

$$I_{ion} = I_{Na_f} + I_{Na_p} + I_{K_A} + I_{K_{DR}} \quad (4)$$

The axonal processes for both type I and type II neurons were modeled as a myelinated, double-cable structure that included nodes of Ranvier (diameter, 1.4 μm), paranodal (1.4 μm) and internodal (1.6 μm) segments, and a myelin sheath (outer diameter, 2.0 μm) (Johnson and McIntyre 2008, McIntyre *et al* 2004, McIntyre *et al* 2002, Miocinovic *et al* 2006). PPN model neurons were not instantiated with synaptic dynamics from axonal afferents given that the distribution, morphology, and type are yet to be established for each cell type. Previous computational modeling studies have indicated that the lowest threshold for generating action potentials using pulse widths at clinical DBS settings (60 - 240 μs) are located in the axonal processes as opposed to cell bodies (Ranck 1975). This process of eliciting action potentials within the axons will be referred to as ‘activation’ in the results to follow, and the stimulation amplitude threshold to elicit action potentials after >80% of the stimulus pulses will be defined as the ‘threshold voltage’.

Finite element modeling of deep brain stimulation

For all DBS lead types, a three-dimensional finite-element model (FEM) of neural tissue was developed around the DBS lead using COMSOL Multiphysics v4.0 (COMSOL, Burlington, MA). The FEM mesh consisted of tetrahedral elements within a 50 mm radius by 80 mm height cylindrical surface with the outside boundary set as the return pathway to ground. Electrical properties of neural tissue were defined as homogenous and isotropic (0.3 S/m), except for a 0.25-mm-thick layer of encapsulation tissue at the electrode surface (0.18 S/m) (Grill and Mortimer 1994). The voltage distribution in the tissue was calculated with a frontal solution method of the Laplace equation, via the stationary MUMPS solver in COMSOL.

The applied stimulus pulse train was based on experimentally recorded waveforms produced by a voltage-controlled implantable pulse generator (Medtronic, Minneapolis, MN). The stimulus waveform consisted of a charge-balanced 90- μs cathodic phase followed by a 3-ms anodic phase repeated at a frequency of 30 Hz, which is consistent with previous clinical studies of PPN-DBS (Ferraye *et al* 2010, Stefani *et al* 2007). The waveform was scaled such that the peak cathodic amplitude at a particular neuron compartment corresponded to the spatial voltage value from the FEM simulations. The waveform was then filtered by a Fourier FEM simulation to incorporate the capacitive properties of the electrode-tissue interface (Butson and McIntyre 2005).

Results

Fiber pathways modulated during PPN-DBS

Computational model predictions of monopolar cathodic stimulation through each of the four electrodes were evaluated for three brainstem fiber pathways that envelope the PPN (SCP, ML, and LL) (figures 3,4). The DBS lead position used for these simulations was consistent with previous clinical studies as noted in the Methods. The two most rostral electrodes (contacts 2 and 3) had the lowest threshold for activation of ML in both the non-human primate and human models. In contrast, caudal electrodes (contacts 0, 1, and 2) generated higher levels of activation of SCP fibers for both models, especially for the two most caudal electrodes. One distinguishing feature of the human model from that of the non-human primate model was the strong activation of LL for caudal contacts 0 and 1. No significant activation of LL at stimulation amplitudes under -6V was found in the non-human primate model, while LL activation could reach nearly 100% in the human model.

PPN cell activation during PPN-DBS

We next quantified the percent activation of PPN cells for each monopolar DBS setting in both the human and non-human primate models, and then compared the results to threshold voltages necessary to activate adjacent fiber pathways (figures 3,4).

The non-human primate PPN-DBS model results indicated that selective activation of a single PPN cell type was not possible using monopolar cathodic stimulation for any of the electrode contacts studied (figure 3). For example, while the models pointed towards an overall lower threshold voltage to activate PPN type II over type I cells (contacts 0, 1, and 3), activation was present across both cell types. For monopolar stimulation across contact 2, the voltage-activation relationship was identical between the two cell types. The location of the DBS lead can partially explain these results. For contacts 1 and 3, the lead was slightly closer to PPN type II axons than to type I axons. In the case of contact 0, PPN type I descending axonal projections were located closer to the DBS lead; however, the type I axons coursed parallel to the DBS lead and thus required higher activation thresholds than the more transverse coursing type II axons. Activating the entire population of either type of PPN neurons was also challenging. Even though contacts 1 and 2 were positioned in the central region of PPN, neither contact was able to activate the entire population of PPN neurons until approximately -5V, which also resulted in activation of ~40-80% of SCP. For the two most caudal electrodes (contacts 0 and 1), SCP activation surpassed PPN cell activation.

In the human model, monopolar stimulation resulted in two distinct activation profiles, corresponding to contacts 2 / 3 and contacts 0 / 1 (figure 4). For contacts 2 and 3, the two PPN cell types had nearly equal activation due to the proximity of these rostral contacts to the ascending thalamic and nigral projections from PPN. Selective activation of PPN cells over adjacent fiber pathways was possible in the human model when stimulating through the rostral contacts. For contact 3, however, achieving a high level of activation of both PPN cell types resulted in activation of a small percentage of ML fibers. Large activation of PPN type II cells was also found for contacts 0 and 1, but was accompanied by over 60% activation of LL and over 30% activation of SCP. Similar to the non-human primate model, PPN type II cells were found to have an overall lower threshold for activation, which again may be due to proximity of the active electrode to the PPN type II population.

Model sensitivity analysis

Consistent stereotactic implantation of DBS leads in the PPN is challenging given the size and depth of the target (Stefani *et al* 2007). Suboptimal clinical outcomes may result if leads are implanted slightly off target (Ferraye *et al* 2010). Using the same implantation angles, the lead was shifted 1 mm anterior, posterior, medial, or lateral (with respect to the original lead trajectory). We then investigated the effects of stereotactic targeting error on fiber pathway and PPN cell activation using monopolar stimulation at -3V (figure 5). A 1-mm displacement was found to have a marked effect on activation in both human and non-human primate models. For example, stimulation via contact 3 in the human model resulted in PPN type I activation ranging from nearly no activation for a posterior or medially shifted lead to nearly 100 percent activation of the population for an anterior or laterally shifted lead. This extreme sensitivity was also found to exist for stimulation via contact 3 in the non-human primate model for both PPN type I and type II cell activation.

Lead misplacement had a different effect in the human than the non-human primate model due to differences in the anatomy. Anterior misplacement in the non-human primate decreased SCP activation by 2% (contact 3) to 24% (contact 1) and increased activation of ML fibers by 18% (contact 1) to 39% (contact 2). LL fibers remained inactivated in all cases

in the non-human primate model. In the human model, moving the lead anterior decreased LL activation by 9% and 35% when contacts 0 and 1 were activated, respectively (the two rostral contacts did not activate LL). SCP activation increased when the lead was moved anterior in all cases, ranging from an 8% (contact 3) to 17% (contact 1) change. PPN type I activation increased for all contacts, while PPN type II activation increased for contacts 0, 1, and 2. In the non-human primate model, DBS lead implantation error had a strong effect on threshold voltages and relative activation results for both fiber pathways and PPN cells. In contrast, in the human model, the fiber pathway results were, in general, more greatly affected by implantation error than were the PPN cells. In both non-human primate and human models, there was no ‘ideal’ lead placement that would selectively activate PPN neurons without concurrently activating at least a small percentage of SCP, ML, or LL fiber pathways. In general, there was a trade-off between complete PPN cell activation and activating a large proportion of the SCP or ML pathways. Since the clinical cylindrical electrode contacts did not provide complete selectivity for PPN cell activation, especially in cases in which the DBS lead was not implanted through the center of PPN, we investigated other DBS lead designs.

Selectivity with radially-segmented electrodes

Given the suboptimal selectivity results with the clinical DBS lead, which consists of cylindrical electrodes, a DBS lead with radially-segmented electrodes was evaluated using the neuron modeling framework (Keane *et al* 2012). Lead placement was chosen based on a cylindrical DBS lead implantation trajectory that yielded suboptimal selectivity in the human model (figure 5, anterior lead placement). Two columns of four electrodes were each activated at the approximate spatial location of contact 3 for the 1-mm shifted anterior lead placement (figure 6a). This combination of active electrodes resulted in an equivalent active surface area to a single electrode on a 3389 DBS lead. For the radially-segmented electrode DBS lead design, the active contacts were chosen on the posterior side to reduce activation of ML (figure 6b). Selectivity of activating PPN over SCP, ML, and LL was compared between the two DBS lead types (figure 6c). The novel lead not only decreased the stimulation voltage necessary for complete activation of PPN type II neurons, but it also decreased the activation of all fiber pathways, resulting in greater selectivity. This example illustrates how radially- and longitudinally-segmented electrodes can facilitate more robust steering of the electric field not only along the lead, but also around the lead.

Discussion

Gait and balance problems, which contribute to falls and lack of independence, are arguably the most debilitating and potentially dangerous motor signs of Parkinson’s disease (Forsaa *et al* 2008, Muslimovi *et al* 2008, Pickering *et al* 2007, Rahman *et al* 2008). Current DBS targets for Parkinson’s disease, such as the STN, have not been conclusively shown to eliminate gait problems for all patients. STN-DBS studies have shown positive results (Johnsen 2011, Johnsen *et al* 2009, Kumar *et al* 1998, Liu *et al* 2006, Shivitz *et al* 2006), mixed results (Xie *et al* 2012), and negative results (Muniz *et al* 2012, Tarsy *et al* 2003) on gait. The PPN is a promising new DBS target for alleviating gait disturbances, given its implicated role in freezing of gait when lesioned (Kuo *et al* 2008) and in the generation of locomotor activity when stimulated (Brudzynski *et al* 1988, Garcia-Rill *et al* 1987, Jenkinson *et al* 2004). In Parkinson’s disease, the PPN is thought to be underactive due to overwhelming inhibitory input from GPi (Aravamuthan *et al* 2007, Gomez-Gallego 2007, Zhang *et al* 2012) and due to neurodegeneration (Jellinger 1988). However, PPN-DBS clinical trials have found inconsistent therapeutic effects in Parkinson’s disease patients (Androulidakis *et al* 2008, Aravamuthan *et al* 2008, Jenkinson 2005, Mazzone *et al* 2005, Plaha and Gill 2005).

The computational models described in this paper provided insight into potential mechanisms underlying these mixed clinical outcomes with PPN-DBS. One possible mechanism could be an incomplete activation of PPN neurons with DBS. PPN type I glutamergic cells have been postulated to play a role in gait initiation (Pahapill and Lozano 2000), whereas PPN type II cholinergic cell activation are thought to be important for modulating locomotion (Brudzynski *et al* 1988). Therefore, both cell types are presumably necessary to provide optimal therapy on parkinsonian gait. The models indicated that achieving complete activation of both cell types would be challenging, especially for type I cells. The models also indicated that stimulation amplitudes above -3V were necessary to activate both cell types for most monopolar electrode configurations. Yet, such amplitudes would likely co-activate fibers of passage.

Another possible explanation for the mixed clinical PPN-DBS results could be an overactivation of fiber pathways adjacent to PPN that would obfuscate the therapeutic effects of PPN-DBS or that would limit stimulation amplitudes to avoid untoward side effects. In the NHP model, the optimal electrode placement to activate both PPN cell types was in the rostro-lateral PPN or slightly anterior PPN. However, in the former case, a significant percentage of ML fibers would be activated concurrently, likely leading to paresthesia side effects. In the latter case, a very large proportion of SCP would be activated, which could have confounding effects on motor control (Iwata *et al* 2004, Rubio *et al* 2004). In the human model, a rostrally active electrode contact was still important, but a lead trajectory through the middle of PPN was the most beneficial for activating both PPN cell types.

Alternatively, the mixed clinical results could stem from another cell group in the MLR (other than PPN neurons) being the optimal target for DBS. Given that clinical studies on PPN-DBS have reported finding rostral electrode contacts in the more therapeutic cases, the cuneiform nucleus or deep mesencephalic region could potentially be a better therapeutic target for stimulation. In our study, the cellular responses to DBS in these regions were not modeled explicitly, but axons projecting from PPN cell bodies did pass through these areas en route to the substantia nigra and thalamus. Interestingly, the modeling results indicated that rostrally stimulated electrode contacts generated the highest degree of activation of both PPN neuron cell types with good selectivity over activation of SCP. The caveat to using rostral contacts, however, was that the higher the stimulation amplitude used, the more likely ML fibers would also be activated, potentially producing paresthesia side effects. This finding will hold regardless of whether the therapeutic target is PPN or other regions in the rostral portions of MLR.

The models also provided opportunities to interpret how deviation in DBS lead placement affect PPN neuron activation sensitivity and selectivity and how such deviations may explain results reported in previous clinical studies. Moro *et al.*, for example, found that all patients in their study reported contralateral paresthesia (Moro *et al* 2010), which based on our models likely resulted from the stimulated electrodes being too rostral, posterior, or lateral to PPN. Ferraye *et al.* noted in their study that the DBS lead targeting was on average 2 mm anterior to PPN with electrodes outside the PPN area (Ferraye *et al* 2010), similar to that presented in our figure 6. The observed side effects from this study included ipsilateral oscillopsia, paresthesia and unpleasant sensations of heat, all reversible with reduced voltage. Our human model suggested that for a 1 mm anterior displacement, only contact 2 would have a promising scenario for selective activation of PPN, which may explain the suboptimal outcomes reported in some patients within their study. Stefani *et al.* (Stefani *et al* 2007) showed lead placement that was lateral and rostral to PPN, with putative implantation in the nucleus peripeduncularis (PPD). The placement that was used and the resulting paresthesia side effects reported is consistent with results from our model, since we also

found that lateral placement of rostral contacts activated a nontrivial portion of ML. The placement used in their study could explain their findings that PPN-DBS had a therapeutic effect on gait given that a significant portion of PPN cells would likely be activated.

While the anatomy of the NHP and human models show similarities (Alam *et al* 2011), prominent differences were evident in the modeling results. Therefore, one should be cautious when interpreting and translating the results of NHP PPN-DBS to human clinical studies of PPN-DBS. This finding is important, given current studies investigating the physiological mechanisms of PPN-DBS in non-human primates (Aziz *et al* 1998, Jenkinson *et al* 2004, Matsumura 2005, Winn 2006). Furthermore, the difference in brainstem anatomy between two humans alone (see (Moro *et al* 2010), Fig. 1) motivates the need for subject-specific models (Butson *et al* 2007). With structures as small as the PPN that are surrounded so closely by fiber pathways carrying non-motor signals, even slight anatomical differences could have large implications on the effectiveness of PPN-DBS therapy. Based on our modeling results, there is little room for implantation error with the current clinical DBS lead design.

The solution to the targeting problem of PPN, and other small DBS target structures, may lie in advancements in DBS lead design. We showed how a DBS lead with radially segmented electrodes could improve activation selectivity of PPN neurons over surrounding fiber pathways. This lead design would provide enhanced flexibility for clinicians, allowing for surgical targeting errors in implantation to be less detrimental to the goal of optimizing therapy for the patient. Additionally, a DBS lead for targeting PPN should be developed with a smaller diameter given that the modeling results indicated that the current clinical DBS lead overlapped with up to 47% of the PPN cells in our models. While additional electrode configurations were not modeled in this study, the increased number of electrodes would provide opportunities to better steer current within the brainstem.

The models do make a number of assumptions that should be noted when interpreting the results. First, the models were developed from histological sections, which may not be representative of the actual sizes and shapes of the underlying anatomy. Future studies that couple our models with high-field imaging data may yield more accurate predictions (Zrinzo *et al* 2011). Additionally, we assumed that PPN cell soma distributions found in the non-human primate are homologous to those in the parkinsonian human PPN. Future histological studies in humans will be helpful for comparing PPN cell morphologies between human and non-human primates (Alam *et al* 2011, Karachi *et al* 2010). Also, the membrane dynamics of the modeled PPN neurons were based on healthy rat electrophysiology, given the lack of equivalent data in the parkinsonian human and non-human primate. We also did not incorporate synapses into the models because their properties have not yet been identified experimentally, which likely produced a conservative estimate of the extent of modulation in the PPN. Finally, it is important to note that a 1 mm displacement of the DBS lead in the NHP model is equivalent to a relatively smaller displacement (~2 mm) in the human model. We modeled the same displacement in both models given that surgical targeting errors are likely to be the same in our experience.

Together, the human and non-human primate models developed in this study provide a new method to contextualize previous clinical studies in patients with PPN-DBS lead implants and compare those results with translational studies in non-human primates. These models also provide a useful surgical planning tool for investigators who seek to optimize PPN-DBS therapy for treating parkinsonian gait disturbances.

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Figure 1.

Anatomical framework for modeling PPN-DBS in non-human primates and humans. Spatial dimensions are given for the (a) non-human primate and (b) human DBS lead and implantation trajectory. (c,d) Modeled fiber pathways that surround the PPN include the superior cerebellar peduncle (red), medial lemniscus (dark green), and lateral lemniscus (light green). Orientation in the human model is different from other figures to provide better view of all fiber tracts. (e,f) Histological reconstructions from (Lavoie and Parent 1994b) showing locations of labeled glutamatergic cells (Type I). (g,h) The equivalent cholinergic cell distribution (Type II) from the same histological studies. L: lateral; R: rostral; P: posterior.

Figure 2.

(a-d) PPN cell morphologies and biophysical responses. (e) PPN neuron models (Type I in magenta, Type II in blue) in the context of both DBS finite element analysis and model responses to a -3V cathodic stimulation pulse train.

Figure 3.

Prediction of neuronal elements activated at $-3V$ cathodic stimulation in non-human primates for each monopolar DBS setting using the clinical lead trajectory. Shown are the fibers of passage (pipes) and PPN soma positions (spheres) activated at $-3V$ cathodic stimulation for all four electrode contacts. Inactivated fibers and cells are not shown. In some cases, activated fibers and cells obscure the active contact, which is depicted in yellow. Additionally, activation profiles are shown for all fibers and PPN cell types for each monopolar DBS setting over a range of stimulation voltages. The dotted vertical line represents the setting depicted on the left.

Figure 4. Prediction of neuronal elements activated at -3V cathodic stimulation in the human model for each monopolar cathodic DBS setting using the clinical lead trajectory. The description of the figure labels is identical to that in Figure 3.

Figure 5.

Model sensitivity analysis of off-target lead trajectories and their effects on activating fiber pathways and PPN cells in non-human primates (top) and humans (bottom). The anatomical images show the trajectory of a DBS lead identical to that used in Figures 3 and 4 (black electrodes), as well as a 1-mm shifted trajectories in the anterior (dark blue), posterior (red), medial (green), and lateral (light blue) directions in both the human and non-human primate models. In both cases, percent activation at each monopolar stimulation setting (-3V) is shown for each fiber and PPN cell type.

Figure 6.

Lead design comparison for improving the selectivity of PPN activation over adjacent fiber pathways for off-target DBS lead implants. (a) Comparison of the clinical cylindrical electrode lead and the revised radially-segmented electrode lead. Active contacts are shown in yellow. (b) Both leads were modeled 1-mm off-target in the anterior direction. Active electrodes in the radially-segmented case faced away from ML in a rostral-posterior direction. (c) Comparison of activation of PPN cells and adjacent fiber pathways using both lead types. LL had no activation below $-7V$ in both models.

Table 1

Active channel properties

Current	Description	g_{ion} (S/cm ²)	
		<i>Type I</i>	<i>Type II</i>
Na _F	Fast-acting sodium current	0.008	0.007
Na _P	Persistent sodium current	0.00001	0.00001
K _{DR}	Delayed rectifier potassium current	0.004	0.004
K _A	A-type potassium current	--	0.001
Ca _T	Low-threshold calcium current	0.0004	--