Thalamic and extra-thalamic connections of the Globus Pallidus in the human brain: The ultradirect pathway

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Abstract

A dominant framework for understanding loss and recovery of consciousness, particularly in the context of severe brain injury, focuses on cortico-subcortical recurrent interactions, with a strong emphasis on excitatory thalamofugal projections. Recent work in healthy volunteers and patients, however, suggests a previously unappreciated role for the globus pallidus pars externa in maintaining a state of consciousness – a finding that is consistent with non-human animal work demonstrating the existence of direct (i.e., extrathalamic) pallido-cortical projections as well as their involvement in modulating electrocortical arousal and sleep. Leveraging on the high-quality Human Connectome Project dataset, we report for the first time in humans, in vivo evidence of (direct) pallido-cortical and pallido-thalamic projections, distinguishing between internal and external pallidal regions. Our data confirm, in humans, the existence of an "ultradirect" extra-thalamic pallido-cortical pathway, with the pars externa connecting preferentially, and extensively, to prefrontal cortex and the pars interna primarily connecting to sensorimotor cortical areas. Furthermore, we also report, for the first time in humans, the likely existence of a direct pathway uniting the globus pallidus pars externa and the medio-dorsal areas of thalamus often implicated in maintenance and recovery of consciousness. Consistent with the pallido-cortical connectivity results, the pars interna appeared to predominantly connect with the sensorimotor areas of thalamus. Collectively, these findings demonstrate the existence in humans of an extra-thalamic "ultradirect" pallido-cortical pathway and suggest a central role of the external segment of the globus pallidum in supporting consciousness.

Introduction

The crucial role of cortico-subcortical interactions in the maintenance of waking consciousness has long been appreciated. Across studies in both healthy volunteers and patient populations, the function of these large-scale interactions has been shown to be modulated by the state of consciousness (Blumenfeld 2012, Kostopoulos 2001, Llinas et al 1998, McCafferty et al 2018, Monti 2012). While the content of consciousness, experience itself, might crucially rely on cortical sites, the thalamus is often considered to play a key role in allowing cortex to generate the type of neural activity that enables conscious experience (Alkire & Miller 2005), perhaps through enabling the delicate equilibrium of dynamic patterns of brain "cross-talk" which might underlie the emergence of specific aspect of information processing in the brain linking distant regions of the brain and/or enabling specific forms of information processing to emerge (Dehaene et al 2003, Demertzi et al 2019, Tononi 2008). Indeed, anesthesia-based loss of consciousness is well known to lead to altered activity in thalamic neurons (Andrada et al 2012), hypometabolism (Xie et al 2011) and decreased thalamo-cortical connectivity (Akeju et al 2014, Liu et al 2013), and a transition from tonic to a more rhythmic bursting firing mode (Silva et al 2010). Furthermore, thalamic stimulation, with many different approaches, has been shown to produce awakening (or faster awakening) from anesthesia (Alkire et al 2009, Alkire et al 2007, Yoo et al 2011) in the animal model. Conversely, thalamic lesions are believed to be associated with loss of consciousness (Castaigne et al 1981) and to be among the most prevalent signatures of protracted unconsciousness in post-mortem studies (Adams et al 2000, Adams et al 1999, Graham et al 2005). Moreover, both thalamic damage (Fernandez-Espejo et al 2011, Lutkenhoff et al 2015) and its de-afferentation from cortex (Lant et al 2016, Zheng et al 2017) have been

demonstrated to be proportional, *in vivo*, to the depth of the impairment in patients with chronic disorders of consciousness (DOC).

Recent evidence, however, suggests that this thalamo-centric view underemphasizes the role of other structures within cortico-subcortical circuits in maintaining conscious wakefulness. Specifically, a growing number of studies involve the globus pallidus – in particular, its external segment (GPe) – in maintaining conscious wakefulness (Lazarus et al 2012, Qiu et al 2016b, Vetrivelan et al 2010). In the rodent model, optogenetic and deep brain stimulation (DBS) of this nucleus led to both increased sleep and EEG delta power (Qiu et al 2016a, Qiu et al 2016b) while cell-body specific lesion of GPe increased diurnal wake and decreased diurnal non-REM sleep (Qiu et al 2010). Moreover, the sleep promoting adenosine A2A receptors found densely in the striatum have been shown to innervate parvalbumin (PV) neurons of the rostral GPe (Yuan et al 2017). In humans, patients with Parkinson's disease exhibit abnormal pallidal function (Bevan et al 2002, Gatev et al 2006, Hutchison et al 1994, Magnin et al 2000, Mallet et al 2008)) and commonly experience insomnia as part of non-motor symptomatology (Gjerstad et al 2007), with etiologies including sleep fragmentation, nocturnal immobility, REM sleep behavior disorder, among others (Chaudhuri et al 2006, Garcia-Borreguero et al 2003, Juri et al 2005, Partinen 1997, Trenkwalder 1998). In addition, findings from human consciousness research further demonstrate an association between the globus pallidus (though the external and internal segments were not differentiated) and level of arousal (Lutkenhoff et al 2015; Crone et al., 2017).

As the second largest component of the basal ganglia (BG), just after the striatum, GPe not only contains extensive connections with BG structures but also direct connections with frontal cortex (Chen et al 2015, Saunders et al 2015) and thalamus (Chattopadhyaya & Pal 2004,

Hazrati & Parent 1991, Mastro et al 2014), both structures crucial for supporting consciousness. It has been proposed that, under the control of the dorsal striatum, direct GABAergic output from GPe to the frontal cortex (Chen et al 2015; Vetrivelan et al 2010) may be an important pathway for sleep-wake regulation (Qiu et al 2010; Yuan et al 2017) though the exact mechanism remains to be elucidated. If indeed direct connections between GPe and thalamus exist, this pathway could also contribute to the influence of cortical activity via the thalamo-cortical route. Thus far, direct GPe connections outside of the basal ganglia have only been verified in animals, but not yet in humans.

In this study, we aim to (i) test the existence in humans of "direct" GPe connections with cortex and thalamus – as assessed with *in vivo* methods, and (ii) contrast the pattern of connectivity of the GPe with that of the GPi, which has long been proposed to be part of the mesocircuit important for recovery of consciousness in DOC patients (Schiff 2010). To achieve these objectives, we employ high angular resolution diffusion imaging (HARDI) data from the Human Connectome Project (HCP; (Van Essen et al 2012)), which offer, as compared to conventional diffusion tensor imaging (DTI) approaches, the great advantage of resolving intra-voxel fiber heterogeneity, therefore providing higher spatial and angular resolution (Tuch et al 2002).

Methods

Data

We analyzed HARDI data provided by the HCP (Q3 Release), WU-Minn Consortium (http://www.humanconnectome.org) (Van Essen et al., 2012). 50 healthy subjects (26 females; 24 males; ages 22-35 years old) were included in the analysis. Imaging data were acquired on a

modified 3T Siemens Skyra scanner. T1-weighted structural (TR = 2400 ms; TE = 2.14 ms; flip angle = 8°; FOV = 224x224 mm; voxel size = 0.7mm isotropic) and diffusion-weighted HARDI (TR = 5520 ms; TE = 89.5 ms; flip angle = 78°; FOV = 210x180 mm; voxel size = 1.25 mm isotropic; 3 shells of b = 1000, 2000, and 3000 s/mm^2 with 90 diffusion directions per shell) data were used. Basic diffusion preprocessing steps have been applied which included B0 image intensity normalization, EPI distortions correction, eddy current correction, motion correction, gradient-nonlinearities correction, and registration of diffusion data with structural (Glasser et al., 2013). Preprocessing was accomplished using FSL tools (http://fsl.fmrib.ox.ac.uk).

Regions of Interest (ROIs)

For cortical and thalamic ROIs, segmented FreeSurfer labels supplied by HCP were used (http://surfer.nmr.mgh.harvard.edu). To create the five distinct cortical zones (prefrontal [PFC], sensorimotor [SMC], posterior parietal [PPC], temporal [TEM], and occipital [OCC]), selected Desikan-Killiany atlas labels were combined together (See supplemental materials) (Desikan et al 2006). Since many of the BG ROIs were not available through FreeSurfer, GPe, GPi, striatum (STR), substantia nigra (SN), and subthalamic nucleus (STN) masks were obtained from the standard (Keuken & Forstmann 2015) probabilistic BG atlas and transformed into individual diffusion space. To refine the GPe and GPi masks, we used the individual whole pallidum FreeSurfer masks as a constraint to define the boundaries.

Probabilistic Tractography

All imaging analyses were accomplished using FSL tools. First, the probability distribution function of fiber orientations at each voxel was estimated with the following

parameters: 3 fibers per voxel, 1000 burn-ins, deconvolution model using zeppelins, and gradient nonlinearities considered. Next, probabilistic tractography was launched with 5000 samples drawn per voxel from each seed mask. For pallidocortical and pallidothalamic connectivity analysis, GPe and GPi each served as a seed mask with each of the five cortical targets and thalamus (THAL) as a waypoint mask, per hemisphere. A contralateral hemispheric mask was also included as an exclusion criterion to limit the connections ipsilaterally. This procedure generated ipsilateral pallidocortical and pallidothalalmic connections, though indirect connections arising from other nearby structures were also considered. For ease of referencing, we will refer to the results of this step as "indirect and direct" connections (IDC). To preclude the influence of indirect connections, we repeated probabilistic tractography with additional exclusion criteria, whereby streamlines entering any of the following masks were discarded: the remainder of BG (STR, SN, STN, and GPe or GPi) and cortical ROIs, thalamus, brainstem, cerebellum, as well as the contralateral hemisphere. The results from this analysis will be referred to as "direct connections" (DC) only. As a final analysis to more precisely visualize the different subregions within thalamus that GPe and GPi may be directly connected with, the thalamus also served as a seed with GPe and GPi as targets, following similar exclusion criteria. Next, the number of streamlines (i.e. connectivity strengths) that successfully reached the cortical and thalamic targets from the pallidal seeds were computed after applying a threshold of 50 (1% of 5000 samples per voxel) (Zhang et al 2014) to remove spurious connections for both IDC and DC. The results were then normalized and rescaled to account for individual differences in seed and target sizes (Eickhoff et al 2010). Individual streamline counts were divided by the total number of samples sent (5000 x seed mask size) and then rescaled by multiplying by the average of all total number of samples sent across all seeds and targets. This step accounted for

differences in seed sizes. Next, the resulting values were then divided by the size of the targets and then again multiplied by the average size of all targets. This accounted for the variability in target sizes. For display of the tractograms, a threshold of 0.01% of the total number of streamlines sent was applied with an additional threshold of least 10% of subjects sharing the tracks. Segmentation of the thalamus based on differential pallidal connectivity was achieved through a winner-take-all approach on the normalized average group connectivity.

Statistical Analysis

Repeated-measures ANOVAs of normalized and rescaled pallidal connectivity values were carried out for IDC and DC with seed (GPe, GPi), target (PFC, SMC, PPC, TEM, OCC, THAL), and hemisphere (left, right) as within-group factors. Upon finding significance, pairwise t-tests comparing GPe and GPi connections were performed along with multiple comparisons correction using the Benjamini & Hochberg (1995) method with false discovery rate set at $q = 0.05$. The new significance cutoff value was thus established at $p < 0.02$. Moreover, percent change of total streamline counts from IDC to DC was calculated.

Results

Assessing Pallidocortical and Pallidothalamic Connectivity Strengths

The total number of streamlines (normalized and rescaled) that successfully reached the cortical and thalamic targets from the pallidal seeds for both IDC and DC are plotted in Fig. 1. Statistical results are reported below:

1. IDC: Significant main effects of seed ($F = 109.063$, $p < 0.0001$) and target ($F = 153.47$, $p < 0.0001$), as well as significant interactions of hemisphere × seed × target ($F = 7.7$, $p < 0.01$),

hemisphere × seed ($F = 11.2$, $p < 0.01$), and seed × target ($F = 46.9$, $p < 0.0001$) were observed. Comparing GPe and GPi connectivity, post-hoc t-tests uncovered significantly higher connections for bilateral GPe-PFC, left GPe-THAL and GPe-TEM than GPi with these targets.

2. DC: Significant main effects of seed ($F = 59.6$, $p < 0.0001$), target ($F = 106.5$, $p < 0.0001$), and hemisphere ($F = 15$, $p < 0.001$), along with significant interactions of hemisphere × seed × target ($F = 15.8$, $p < 0.0001$), hemisphere × seed ($F = 34.5$, $p < 0.0001$), hemisphere × target ($F = 18.9$, $p < 0.0001$), and seed × target ($F = 51.7$, $p < 0.0001$) were detected. Post-hoc comparisons revealed significantly greater connections for bilateral GPe-PFC and GPe-THAL, left GPe-SMC, GPe-PPC, and GPe-TEM than GPi with these targets.

Overall, while the general pattern of DC remained roughly the same as IDC after introducing comprehensive exclusion criteria to minimize the influence of indirect connections, the direct connectivity values reduced drastically, with up to 96% decrease from IDC to DC, with GPi appearing to suffer more than GPe for the most of the connections (Fig. 1). We evaluated relative residual direct connectivity strength by separating the total streamline counts (tSC) into 3 categories: high (tSC > 10,000), medium (5,000 – 10,000 tSC), and low (tSC < 5,000) probability of connection. THAL, SMC, and PPC all exhibited medium to high probability of direct connections with GPe and GPi, but only GPe, not GPi, demonstrated a high likelihood of direct connection with PFC. Additional low direct connectivities were noted for pallidal connections with TEM and OCC regions.

Topographical Organization of GPe and GPi Connections

Since our primary interest lies in direct connections, the descriptions hereafter will pertain only to DC. Group pallidal projections to the different cortical and thalamic targets as

well as corresponding pallidal seed voxels with robust target connectivity are displayed in Fig. 2. Similar topographical connectivity patterns were identified for GPe and GPi, with the exception of PFC and THAL connections. While GPe-PFC connections covered the entire prefrontal target and originated from pallidal voxels concentrated mostly in the anterior subregion of GPe, GPi-PFC connections mainly projected to the posterior border of PFC (presumably, association motor cortices) and localized within the posterior subregion of GPi. Similar subregions of the GPe (anterior and a small posterior cluster) and GPi (posterior) corresponded to strong connections with THAL. Furthermore, SMC, PPC, TEM, and OCC connections resided primarily in posterior portions of GPe and GPi. Given the difficulty of dissociating preferential targeting in the thalamus from individual pallidothalamic tracks, connectivity-based segmentation of THAL with respect to GPe and GPi revealed distinct patterns of disparate pallidal organization within thalamus (Fig. 3). Namely, GPe connections occupied more medial aspects of thalamus, predominantly including putative midline, mediodorsal (MD), intralaminar (IL), and ventral anterior (VA) nuclei, with the highest concentration in the central medial intralaminar nucleus (CeM); GPi connections, on the other hand, were found in more lateral and posterior portions of thalamus, reflecting primarily ventral lateral (VL), ventral posterior lateral (VPL), ventral posterior medial (VPM), lateral posterior (LP), pulvinar (PUL), as well as some IL nuclei, with peak connections in VL motor thalamus. While both pallidal connections within THAL covered intralaminar nuclei, comparatively, GPe was more connected with central lateral (CL), central medial (CeM), and parafasicular (pf) nuclei, and GPi with centromedian (CM).

Discussion

We used probabilistic tractography with comprehensive *a priori* exclusion criteria to characterize, for the very first time in humans, the pattern of direct pallidal connectivity with cortex and thalamus, separating its internal and external compartments. Overall, our findings of direct (i.e., extra-thalamic) connections between the GPe and prefrontal cortex and direct (i.e., not STN/GPi-mediated) connection to thalamus are not only consistent with animal studies (Chattopadhyaya & Pal, 2004; Chen et al 2015; Hazrati & Parent 1991; Mastro et al 2014; Saunders et al 2015), but also revealed novel findings including additional probable direct pallido-cortical connections and uncovering very different patterns of prefrontal and thalamic connectivity across the GPe and GPi. Indeed, the two compartments of the GP clearly mapped onto differential patterns of (direct) cortical and thalamic connectivity. A strong, widespread coverage of GPe tracks into the PFC, as compared to the weak GPi tracks, restricted to the posterior border of PFC (presumably, a partial association motor area). These pallido-PFC tracks also originated from different subregions of the pallidum, with anterior GPe corresponding to GPe-PFC projections, and posterior GPi representing GPi-PFC connections. Anterior GPe has been reported to connect with the prefrontal cortex (Francois et al 2004, Grabli et al 2004), whereas the posterior portion of GPi has been well established as a sensorimotor region (Visser-Vandewalle et al 2009). While the strong, direct GPe-PFC would still survive a more stringent thresholding, the weak, direct GPi-PFC connectivity would most likely fail. The direct GPe-PFC connections are validated against animal tracer studies and are thus likely to exist, but direct GPi-PFC connections may be more limited and if present, perhaps, exclusive to sensorimotor regions. Of course, given the structural nature of our methodology, the role of the direct GPe-PFC pathway, in humans, remains speculative. Findings from animal studies suggest that GPe may be involved in regulating sleep-wake (SW) behavior and cortical activity (Qiu et al 2016a, Qiu et al

2010, Qiu et al 2016b, Vetrivelan et al 2010). GPe lesions in rodents produced a 45% increase in wakefulness and significant slowing of cortical EEG (Qiu et al 2010), while DBS and optogenetic excitation of GPe neurons have been shown to directly promote sleep (Qiu et al 2016a, Yuan et al 2017). Confirming a separation between the duties of the two compartments of the pallidum, lesions to the GPi did not significantly change SW activity (Qiu et al 2010).

In addition to the direct pathway from GPe to frontal cortex, a direct connection between GPe and thalamus may also have important implications in disorders of consciousness. The mesocircuit hypothesis of DOC posits that following structural damages, functional disruptions at the BG-THAL level may also occur, leading to a reduced excitation of the anterior forebrain (Schiff 2010). Thalamo-prefrontal connections have been advocated to be necessary for sustaining organized behavior during wakefulness (Schiff 2008) and consistently implicated in DOC (Laureys et al 2000, Monti et al 2015, Zheng et al 2017). Yet, the current hypothesis fails to factor GPe into the model and attributes the reduced cortical excitation to the undertaking of the GPi through its excessive inhibition supposedly on the central thalamic nuclei (intralaminar complex and adjacent paralaminar portion of association nuclei—MD, VA, VL, and PUL) following insufficient inhibition from the striatum. Nonetheless, we could not find a study to date presenting evidence indicating that GPi may be the pallidal structure responsible for the down-regulation of frontal activity. In fact, due to the difficulty of separating the pallidum into internal and external parts from limited resolution, studies investigating DOC have only reported the globus pallidus as whole to be involved. For example, DOC patients, compared to controls, showed reduced metabolisms in the striatum and central thalamus yet increased metabolism in the globus pallidus (Fridman et al 2014). Moreover, behavioral arousal in chronic DOC patients has been shown to be negatively correlated with degree of atrophy in the dorsal striatum and

globus pallidus (Lutkenhoff et al 2015). In the anesthesia model, once direct pallido-cortical connections were included in the directed connectivity modeling, propofol-induced loss of consciousness was found to disrupt pallido-cortical, but not thalamo-cortical connectivity (Crone et al 2017). These observations emphasize a critical role of the globus pallidus in supporting consciousness and do not preclude the possibility that GPe may be a vital contributor.

Nevertheless, our findings offer support for GPe as a potential influencer in the mesocircuitry. The direct connection between GPe and PFC, as shown in our results and prior animal studies, may serve to suppress neurons in the frontal cortex, though it is unclear whether the targets are pyramidal neurons or interneurons, or both. Another indication of GPe being intimately involved with PFC is evident in the pallidal connectivity based segmentation of the thalamus, where GPe displayed a greater preference for medial thalamus, which contains the main prefrontal projecting thalamic nucleus—MD (Klein et al 2010) and also a part of the central thalamus. Impairment in the mediodorsal nucleus stands as one of the most replicated findings in the DOC literature (Fernandez-Espejo et al 2010, Hannawi et al 2015, Lutkenhoff et al 2015, Lutkenhoff et al 2013, Monti et al 2015, Zheng et al 2017). Furthermore, the strongest thalamic connection with the GPe was detected in the central medial nucleus, a component of the anterior intralaminar complex. Receiving inputs from the brainstem and basal forebrain, the anterior intralaminar and mediodorsal thalamus have been postulated to assume a role in arousal regulation and possibly extending to awareness (Schiff 2008). On the other hand, GPi was most connected with ventral lateral nucleus, implying a more motor-related function, consistent with the classic role of GPi. This is additionally reflected in GPi's projections to more motor parts of the frontal cortex.

Administration of zolpidem, a selective GABA-ω1 (a subunit of GABA-A receptor complex) agonist commonly used to treat insomnia, has produced paradoxical effects in DOC patients that have led to increased arousal and cognitive performance (Chatelle et al 2014, Clauss & Nel 2006, Clauss et al 2000, Shames & Ring 2008, Whyte et al 2014). Although the mechanism of action of this paradoxical response is largely unknown, the notion that zolpidem could act on the GABA-A receptors found abundantly in the globus pallidus to shut down its inhibitory output has been considered. Seeing that both GPe and GPi may contain large numbers of GABA-A receptors (Xue et al 2010), and that differing patterns of frontal and thalamic connectivity exist between the two pallidal structures, we propose that zolpidem's action on GPi may, if detectable, improve more motor-related aspects of behavior, whereas zolpidem's target on GPe may underlie the actual arousal and possibly cognitive increase observed in the DOC patients as GPe has been implicated in arousal regulation and is robustly connected with higher-order cognitive areas. Additional evidence alluding to a greater likelihood of GPe than GPi in contributing to the positive effects of zolpidem stems from findings that collectively demonstrate changes in prefrontal activity following administration of zolpidem in DOC patients who responded to the medication (Brefel-Courbon et al 2007, Chatelle et al 2014, Clauss et al 2000, Williams et al 2013). Again, GPe's preferred connections with the PFC directly, and indirectly through the medial thalamus, strengthen our hypothesis. An update to the mesocircuit hypothesis with inclusion of the GPe is thus needed.

We found additional probable direct connections for both pallidal structures with SMC and PPC, although there currently lacks evidence from animal studies to validate these findings. These pallido-cortical connections originated from the posterior portions of the pallidum, which is consistent with DTI findings in humans from Draganski et al (2008), but the authors did not

use exclusion criteria to limit indirect connections. However, while quantitatively different, DC (direct connections) versus IDC (indirect + direct connections) may remain qualitatively similar, sharing the same topographical patterns of connectivity.

Using diffusion imaging to infer the existence of connections between regions presents many challenges, especially for determining "direct" connections. Currently, one of the only ways of approaching the delineation of "direct" connections relies on strategically implementing exclusion criteria based on some a priori knowledge. However, the selection of exclusion criteria stands to be difficult and presents a tradeoff. On the one hand, not adding enough exclusions may still be subjected to the influence of indirect connections, but on the other hand, including too many exclusions may be overly stringent and lead to false negatives. Because our primary goal was to demonstrate the existence of "direct" connections, we opted for extensive exclusion criteria, albeit overly stringent, in hopes of removing as much of the indirect connections as possible. Though there could still exist some indirect connections in our "direct" connectivity results, the majority of which are likely addressed. On a general note, the inability to differentiate afferent and efferent connections remains a major limitation of diffusion tractography, although animal tracer studies suggest an output pathway from GPe to PFC and potentially bi-directional connections between GPe and thalamus.

Conclusions

We demonstrated with probabilistic tractography using HARDI data provided by the HCP that direct GPe connections with PFC and THAL are likely to exist in humans, concurrent with animal tracer studies. These direct GPe connections also exhibited differing patterns of frontal and thalamic connectivity when compared against GPi. Favoring connections with

distributed prefrontal cortex and medial thalamus, GPe is situated in a position to influence key aspects of consciousness. Conversely, GPi, preferring connections with more motor-related regions, remains a central player in the regulation of motor control. The current findings urge for an update to the mesocircuit hypothesis with the incorporation of GPe to shed light on the mechanisms underlying disorders of consciousness.

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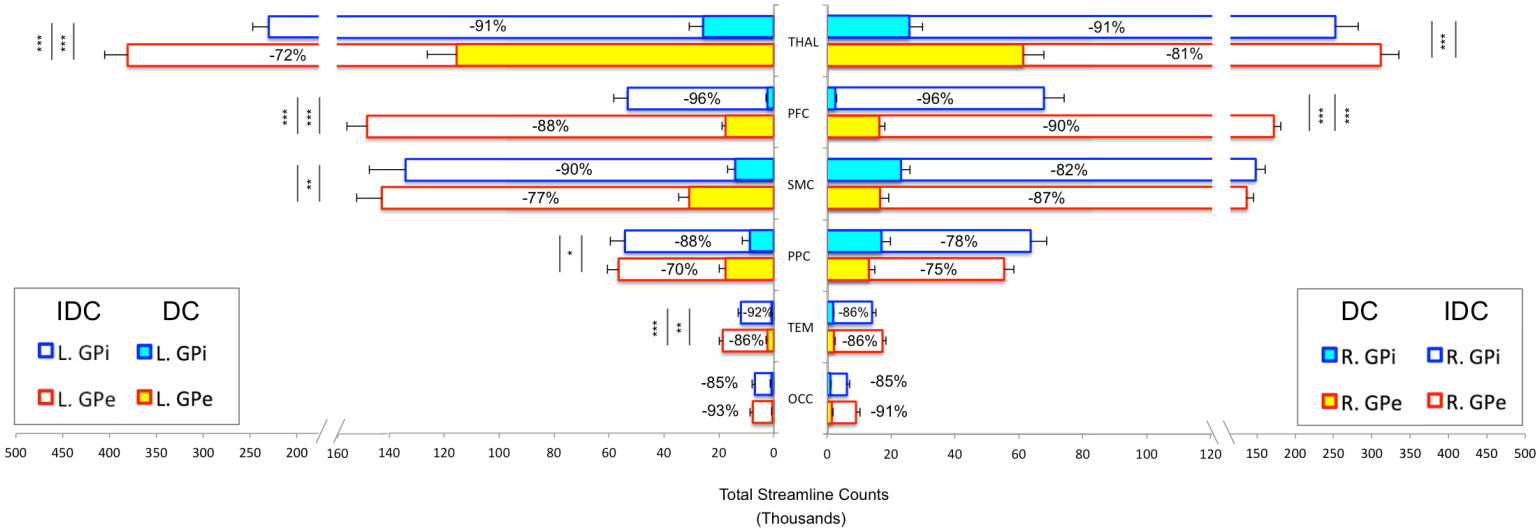
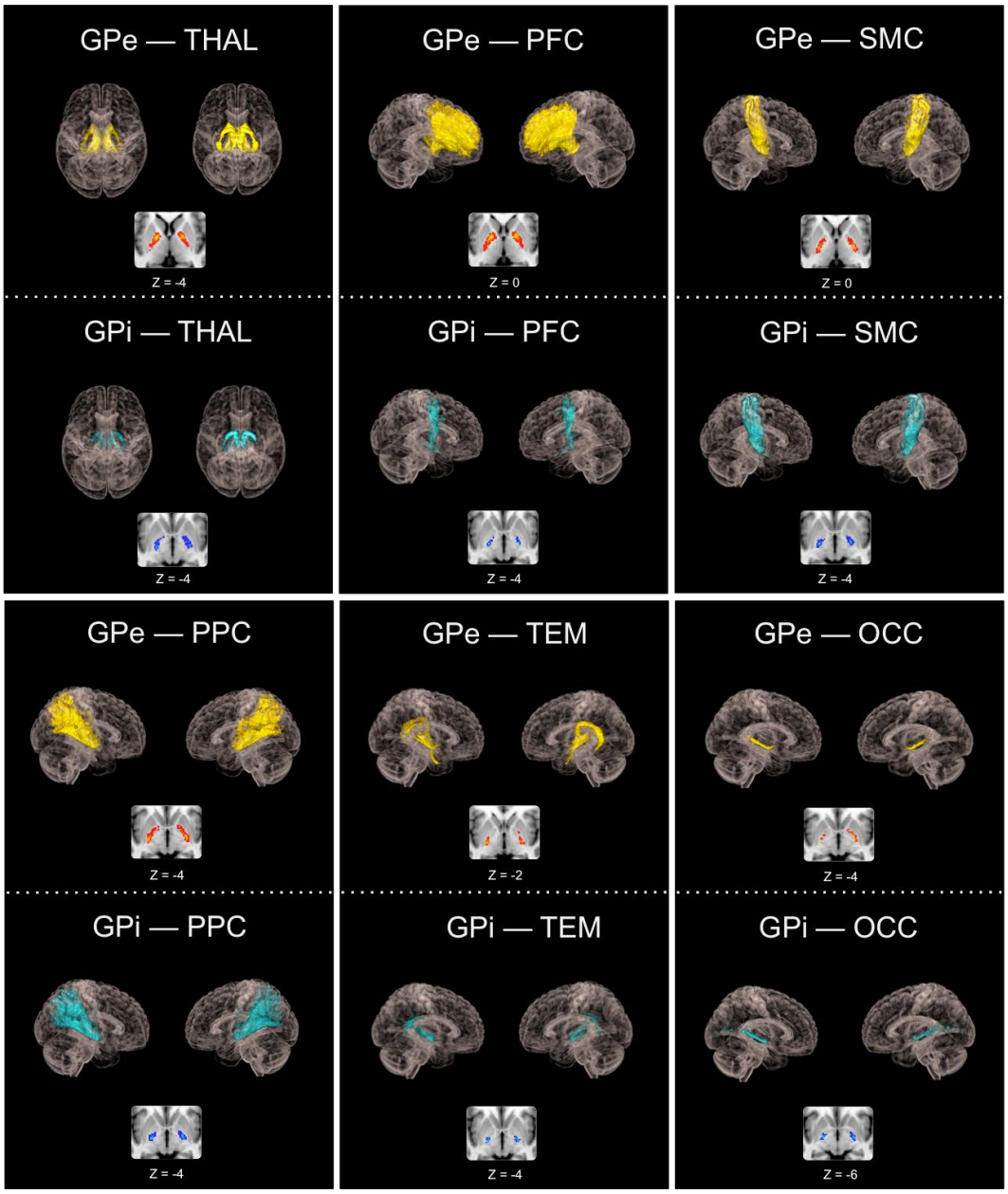
Figures

Figure 1. Pallido-cortical and pallido-thalamic connectivity strengths



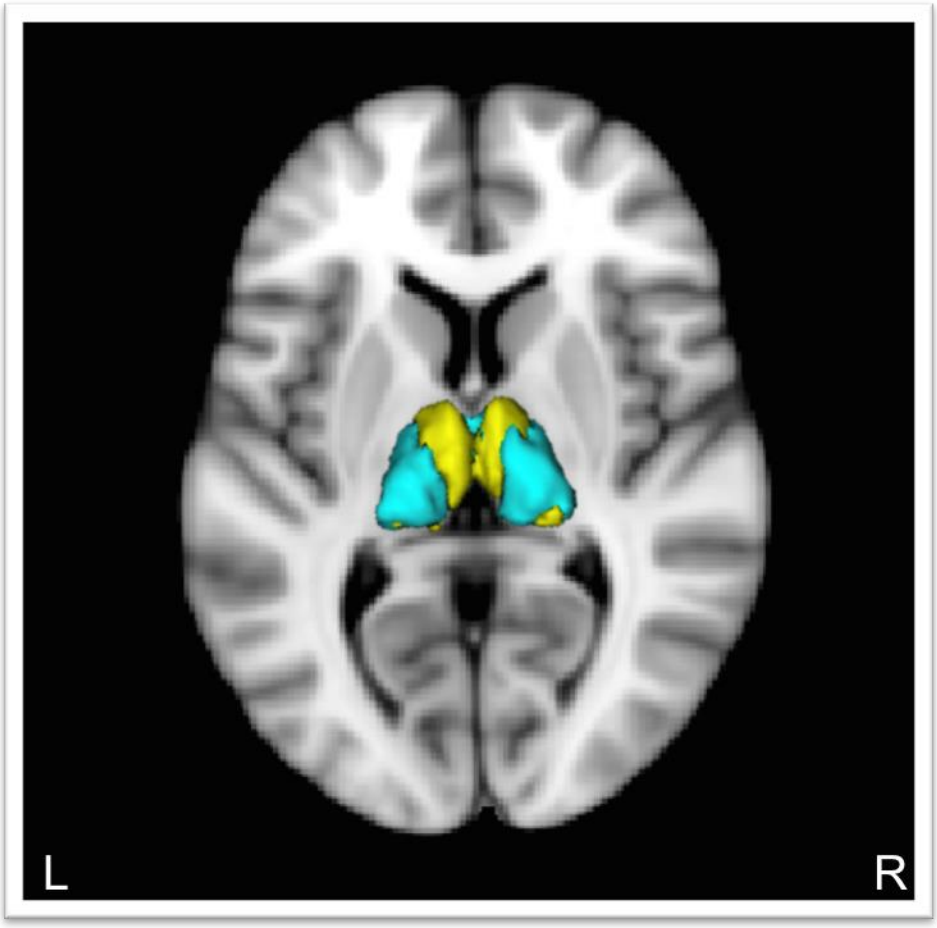
Connectivity strengths as assessed by the group averages of total streamline counts between each seed and target ROI (normalized and rescaled) are plotted. DC (direct connections) and IDC (indirect and direct connections) are overlapped to reflect a percent decrease going from IDC to DC. GPe and GPi connections are statistically compared, with significance denoted using inner asterisks to correspond to DC and outer asterisks to IDC.

Figure 2. Topographical patterns of direct pallidal connectivity



Top sections show reconstructed pallidal pathways, and cropped axial images below reflect preferred subregional connectivity originating from GPe or GPi.

Figure 3. Segmentation of thalamus based on connectivity with GPe and GPi



Yellow = GPe connections within thalamus. Blue = GPi connections within thalamus

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