Changes in PD due to DBS

remy.rhoades

Daniel Uy

John A Thompson

# Abstract

Parkinson’s Disease is a neurodegenerative disorder diagnosed by neurodegeneration of dopaminergic neurons in the striatum and can present as motor symptoms including bradykinesia or akinesia and rigidity, tremor-at-rest, or instability, and cognitive, olfactory, and mood symptoms. Patients with PD become candidates for surgical intervention once other treatment options, such as medication, have been exhausted. Deep brain stimulation or DBS is thought to relieve symptoms by overriding or disabling activity of the target region, commonly the subthalamic nucleus or STN. While DBS has been shown to treat PD symptoms, the mechanism of its efficacy is not definitively understood. Here we examine studies of the effect of DBS on PD brains, focusing on connectivity, electrophysiology, and plasticity. Based on reported research, we elaborate on increases in functional connectivity of DBS target with related structures due to DBS. Additionally, DBS attenuates pathological electrophysiological oscillations in PD disease state towards a healthy state. Lastly, the synaptic and intrinsic plasticity of the premotor and motor cortices may normalize due to DBS. These points impress upon audiences that DBS may incur efficacy via multiple means, but for further consideration is whether DBS improves function or also repairs pathological reorganization and compensation mechanisms due to disease. As a mechanism of PD is dopaminergic neurodegeneration, does PD halt degeneration or does it treat the symptoms?

# Introduction

        The medical community has not established an accepted understanding of Parkinson’s Disease etiology. Deep brain stimulation, or DBS, treats symptoms of PD through an unknown mechanism. At this time, researchers propose that stimulation creates a virtual lesion of the target region as compared to earlier methods of physically lesioning the region. Commonly-targeted structures of DBS include the subthalamic nucleus, STN or globus pallidus internal segment (GPi) (Przedborski 2017). PD causes motor, cognitive, olfactory, and mood symptoms with motor manifestations including bradykinesia or akinesia and rigidity, tremor-at-rest, or instability. Neurally PD is marked by neurodegeneration and death of dopaminergic neurons in the striatum (Kuramoto et al. 2013). PD gradually progresses in stages, with extensive progression potentially preceding manifestation of clinical symptoms (Nandhagopal et al. 2011). Various sources document remaining effects from DBS subsequent to DBS off lasting for atleast 10 years (Castrioto 2011). Maintenance of treated clinical symptoms or status when deep brain stimulation was turned off suggest long-term changes.

        In the development of disease state, PD brains attempt reorganization and compensation to function (Kuramoto et al. 2013). Years of subsisting on crutch methods may be the tactic of the PD brain. Mechanisms of compensation include increased synthesis and release of dopamine (DA) from remaining DA neurons and reduced rate of DA inactivation to compensate for the extensive loss of dopaminergic neurons (Zigmond et al. 1990). Compensation in substantia nigra includes activity increase in the pars compacta (Blesa et al. 2017). Also, reorganization may alter connectivity in individuals with PD to maintain a level of functionality. While DBS therapy can not reinstate prior numbers of cells, stabilizing levels of dopamine and assisting in other areas can provide relief. Therefore, while DBS may not rehabilitate the system entirely, the changes incurred hopefully stabilize function and promote health.

         PD Patients usually become candidates for surgical intervention once other treatment options, including medication, have been exhausted. DBS implantation of STN or, less commonly, GPi, likely immediately mediates symptoms. Although cognitive and emotional symptoms may remain or increase, patients usually experience improvement in symptoms. A factor in considering DBS surgery, responsivity to dopamine, further verifies patient diagnosis of Parkinson’s Disease as opposed to a separate motor disorder. Dopamine, in the form of levodopa, is tested in patients in the decision for DBS surgery. Also, health professionals tailor DBS stimulation parameters to individual patients.

        In this review, we will examine connectivity, plasticity, and electrophysiology changes incurred on the brains PD of patients by DBS. We will review studies on electrical oscillations in disease state and DBS. Importance of normal electrophysiological fluctuations correlated with relevant neighboring brain regions will be considered. Then, we will examine connectivity patterns in PD brains due to disease and DBS. In light of disease impact, we will discuss functional and structural connectivity changes and network trends due to DBS. Finally, we will explore plasticity in perpetuating disease-state patterns and in recovery. We will discuss the physiological materials for and development of neuroplasticity and its implications for electrical behavior. Overall, we will summarize findings on the degree of recovery due to DBS and the issues that DBS patients may face.

***Anatomy***

        The implications for DBS’s effect of connectivity can be traced to vast functional and structural connectivity of striatum with brain regions. Brunenberg et al. cite STN subregions as cognitive, motor, and associative  (Brunenberg et al. 2012). Variables for consideration include functional and structural connectivity, directionality of tracts, and intent of connections as information transfer or data modulation. Additionally, a feedback pathway exists from cortex to striatum, as compared with the primary path from the striatum to cortex. Furthermore, analyzing within-striatal and extrastriatal connectivity addresses two main types of network breakdown in PD. Connectivities between many extra-striatal networks were found to break down in Parkinson’s disease in a similar manner to the pathological decoupling of the striatal network (Bell et al. 2014). Some groups suggest pyramidal tract cortical neurons to be a primary mechanism by which STN stimulation antidromically affects cortex via the hyperdirect pathway (Shepherd 2013). Researchers identify striatum as particularly amenable to functional changes but not structural due to stimulation. PT neurons innvervate ipsilateral striatum, thalamus, and/or brainstem. While assumption that the direct STN-cortical pathway conduct the current, antidromic activity from STN via PT neurons may contribute more (Li et al. 2012).

         Varying methods to study connectivity between brain areas allow for thorough approaches to connectivity research. One may choose modeling, imaging, or an interventional method such as stimulation. Imaging includes diffusion tensor imaging (DTI) and functional magnetic resonance imaging, or fMRI. Investigators use DTI to reconstruct white matter tracts while fMRI analyses reveal functional connectivity between isolated brain regions or groups. Transcranial magnetic stimulation, or TMS, involves a magnetic field generating an electric current in the target area to affect electrical activity of underlying tissue. TMS results may indicate excitability of cortical gray matter and/or the integrity of white matter underlying affected tissue. Computational models of connectivity permit investigators to more flexibly approximate relationships and behavior, especially considering physical barriers recording from deep subcortical regions. Thus, multiple measurements and technologies allow for analysis of connectivity, particularly of subcortical regions whose position and extensive connections may suffer from one approach. Estimation of network dynamics, ranging from such systems as subcortical to default network functional connectivity provide valuable data on connectivity changes due to DBS.

            Functional and structural connectivity may serve to both propagate dysfunction in disease and promote recovery in intervention with DBS. Functional connectivity of STN with motor cortex has been shown through DBS (Devergnas and Wichmann 2011). Prior to DBS, connectivity of the diseased striatum conducts hypofunction to other regions, as evidenced by higher cortico-subcortical connectivity correlated with cortical atrophy (Yau et al. 2017). Physically, networks and tissues that survive disease may serve as conduits for DBS current. As such, the existing integrity of white matter underlying frontal regions, particularly motor regions, affects DBS outcome (Horn et al. 2017). Additionally, the integrity of frontal cortex, indicated by cortical thickness, affects the clinical outcome of DBS (Muthuraman et al. 2017). Existing connectivity provides the scaffold for activity resurgence with DBS but correction of disease state must also be considered. With DBS, Parkinsonian patients on DBS and off medication have shown increased M1–STN connectivity (Baudrexel et al. 2011). Thus, propagation of striatal dysfunction in disease state becomes conducting activity with DBS for improvements. We must consider connectivity as a means of dysfunction in PD and improvement with DBS using existing structures and connected networks.

        Hemispheric differences in prefrontal and dopamingeric function may influence the effects of DBS. Tucker and Williamson found that dopaminergic asymmetries in innervation underlie functional differences (Tucker and Williamson 1984). Dopamine is significantly left-biased and brains that are dopamine deficient were left-biased, implying PD function is dopamine left biased. With the addition of DBS, usually implanted on the left side first, we could maximize the effect given preexisting asymmetry. “The relationship between dopamine levels and left-right asymmetry suggests that brain asymmetry is a dynamic process, depending in part on the activity of the particular system as a whole (Glick, Ross, and Hough 1982).” Implanting one side may have different effects than bilateral implantation, given time elapsed between surgeries too. Overall, brain asymmetry has large implications for differences in function due to DBS based on connectivity. Additionally, while many investigators state that structural asymmetry increases with age, Cabeza finds that functional prefrontal asymmetry decreases (Cabeza 2002). High-performing elderly humans recruit less asymmetrical frontal regions in cognition compared to low-performing seniors in order to compensate for age-related inefficiency (Cabeza et al. 2002). Studies claim PD patients exhibit worsening cognitive scores before and after DBS, likely due to cognitive degeneration and aging (Mehanna et al. 2017). While DBS could change executive function and emotion, clinicians must propose alternate methods to address these (Combs et al. 2015).

         The many regions innervated by the BG, and the complexity of those connections imply extensive capability for change. On a global scale, Deco et al. report “rebalancing of functional brain networks” in response to 6 months of STN DBS (van Hartevelt et al. 2014). One group measured higher communicability and coherence during DBS compared to DBS-off (Saenger et al. 2016). In measurements of resting state functional connectivity, DBS rebalances resting state functional networks (Kringelbach, Green, and Aziz 2011). Connectivity changes may be influenced by extensive neuromodulatory connectivity from subcortical regions to the PFC (Dembrow and Johnston 2014). A group modeled STN DBS to have widespread influence including extrinsic direct, indirect, hyperdirect, thalamo-cortical, as well as cortico-striatal pathways (Kahan et al. 2014). Additionally, increased connection strength was found to correlate with improvements in clinical ratings of motor function.

***Electrophysiology***

        Abnormal electrophysiology is one of the most thoroughly-researched indications of PD pathology. An important consideration in PD pathology becomes exaggerated or magnified oscillatory behavior. Exaggeration of natural beta and gamma oscillatory frequencies reflect pathology or dysfunction of basal ganglia (Hammond, Bergman, and Brown 2007). Findings that beta and gamma/theta activities reflect respective brake and accelerator functions attributed to the basal ganglia support speculation that PD exhibits magnification of inherent frequencies (Jha et al., n.d.). Groups claim that, despite a small worsening of movement induced by STN DBS, improvement from removal of noisy beta signal indicates the primary role in pathology (CHEN et al. 2007). One mathematical method to quantify if two or more brain regions have similar neuronal oscillatory activity with each other is called coherence (Bowyer 2016). Coherence and communicability, two popular terms to describe network dynamics, will gauge facilitation of information transfer across regions. Subsequently, healthy network activity and interactions between brain regions may be interrupted as regions electrophysiologically decouple. Regarding, cortical function, beta rhythms are implicated in the activity of distant brain networks during a “perceptual or cognitive task” (Deco, Roland, and Hilgetag 2014). Researchers implicate gamma oscillations in “consciousness, perceptual binding, and other higher order cognitive functions.” Thus, pathological exaggerations of natural oscillation frequencies influence a range of regions.

        The brain as a system develops in and considers weak signals and noise as factors in its natural state. Prior to DBS, heightened beta oscillations may overshadow other activity that is viable in normal state. In light of DBS, networks and groups may consider weak signals and noise for activity due to removal of excessive beta oscillations. As such, human sensorimotor control in a healthy state considers noise when executing behaviors (Faisal, Selen, and Wolpert 2008). To optimize behavior, for example, we “choose to move in a way that reduces the detrimental consequences of noise.” This concept is called the stochastic optimal-control theory of sensorimotor control. Allowing for deviation from a plan to more efficiently achieve the task shows the use of prior knowledge and averaging in motor behavior. Variation, noisy and from the environment, modulates execution of plans via optimal feedback control in completing the task goal. In disease-state PD,  while a few frequencies such as beta and gamma dominate signal, silencing of weak signal and noise may impair activity. Environmental input guiding precision in motor movement would be drowned out by excessive frequencies. As we established extra- and intrastriatal networks decouple in PD, there becomes less opportunity for noise to amplify via group activity. This concept, called stochastic resonance, is a process by which noise facilitates transmission of already weak signals. Impaired network connectivity implies weaker signals such as environmental stimuli have less opportunity to influence behavior. Deco emphasizes the role of weak signals and noise, containing no information but influencing activity, on coupled clusters of activity (Deco et al. 2009). Thus, detection of activity in light of elimination of excessive pathological activity may be how DBS improves motor behavior and opens opportunity to regain other function.

        While we claim pathological basal ganglia oscillations to characterize PD pathology, secondary or peripheral effects may arise due to network connectivity. Additionally, given the connectivity between subcortical and cortical regions, the extent of the impact of frequency oscillations could confer far-ranging effects. Innervation by subcortical areas of cortex when stimulated by DBS pose an opportunity for widespread effect. Large myelinated white matter tracts transmit current well and often impact distant functionally and/or anatomically connected regions.  An important consideration is the physical properties of tissue propagating or receiving current stimulation. Findings from transcranial electrical stimulation show varied cortical tissue thickness may distribute current differently and require different current strength to achieve the same effect (Muthuraman et al. 2017). Cortical excitability may vary with age, circadian rhythms, hormonal levels, and other factors (Krause and Kadosh 2014). In addition, axonal integrity of patients may vary starting at implantation and differ in response to DBS. Concerning the effect of white matter microstructure of cortical excitation, Groppa et al. found that cortical excitability from dual-site TMS was directly influenced by underlying white matter microstructure as measured by DTI (Groppa et al. 2012). They used regional fractional anistropy as an indication of microstructural integrity which depends on the degree of myelination, axon diameter or axon density and considers “multiple microstructural properties of regional white matter such as the homogeneity of fiber orientations within a given voxel, axon density, the amount of myelination, and axon diameter.” The stronger influence of axial fibers led them to posit that an increased number or density of axons in the subcortical pathway connecting cortical regions of interest might account for stronger cortico-cortico facilitation.

***Plasticity***

      At the cellular level, the cortico-subcortical motor circuit inherently uses plastic mechanisms to learn and execute motor plans (COSTA 2007). Dopamine, decreased in cell degeneration, functionally underlies plasticity in motion and learning (Shen et al. 2008)(Quraishi and Paladini 2017). As a result of decreased dopamine, striatal medium spiny neurons lower their thresholds as a homeostatic plastic mechanism to retain function (Azdad et al. 2009). Additional mechanisms include plastic alteration of frontal cortical regions to accommodate decreased subcortical output. Pascual-Leone states that plasticity may have a harmful effect in chronic degeneration as systems inflict widespread change to adapt (Pascual-Leone et al. 2005). Therefore, long-term bilateral DBS may eliminate the need for compensatory mechanisms and protect surviving dopaminergic substantia nigra neurons (Temel et al. 2006). DBS may permit stochastic activity and noise detection through reduction of excessive beta frequency, reinstating potential for varying plastic processes to occur. Spontaneous activity supplies the raw material for plastic change such that DBS may facilitate healthy levels of plasticity (Kerschensteiner 2013)(Fox and Raichle 2007).  As Bach-y-Rita showed in the ’90s, motor plasticity is use-dependent (Bach-y-Rita 1990). Recovery of motor function is possible.

          In disease-state PD, premotor and motor cortical levels of excitability depend on whether the patient is akinetic or dyskinetic. In reference to development of PD, death of dopaminergic neurons and dysfunction of BG oscillatory activity may impact cortex, leading to lower cortical excitability in supplemental motor, etc. regions (Frackowiak et al. 2003). Conversely, in patients with levodopa-induced dyskinesia, hyperexcitability of premotor and motor cortex due to medication accounts for excess movement and is symptomatic of excess cortical excitability (Rascol 1998). This has been proven by rTMS studies where low frequency rTMS was applied over supplementary motor area in dyskinetic patients to decrease excitability (Koch et al. 2005). The implementation of DBS normalizes subcortical dysfunction allowing for cortical hypoexcitability to subside (Fraix et al. 2008). By rendering plastic compensatory mechanisms unnecessary, consequently, DBS may free up energy from motor, premotor, and other cortices for other processes. Given the expenditure of resources on maintaining function sans input in the regions, one would expect capability for other functions to free up. Elkohon Goldberg, referring to the frontal lobes’ fragility in succumbing to disease in The Executive Brain, states the “frontal lobes’ unique vulnerability is the price they pay for the exceptional richness of their connections.(Goldberg 2002)” Furthermore, Goldberg references the “noise summation” effect wherein aberrant signals sum in prefrontal cortex following damage. Additionally, damage could be local but, most likely, is a remote effect from elsewhere.

       Two mechanisms by which plasticity originate include intrinsic and synaptic plasticity, referring to the origin of efficacy. Synaptic plasticity incurs change at synapses between neurons and whereas intrinsic plasticity alters the efficacy of whole neurons. Thus, synaptic plasticity may cause change in more isolated groups of cells or tissue than intrinsic plasticity. Beck et al. elaborate on intrinsic plasticity as a possible mechanism by which widespread change can occur in a pathological state (Beck and Yaari 2008). Camp cites damage or impairment of function as an impetus for intrinsic plastic alteration, suggesting intrinsic change in PD (Camp 2012). One form of synaptic plasticity, a means by which synaptic strength increases due to brief, high-frequency stimulation of a small group of synapses, is termed long-term potentiation, or LTP. Understandably, the nature of DBS lends itself to incurring LTP in connected cells (Zhang and Linden 2003). We can deduce that HF current promotes LTP and, thus, relevant neurons experience strengthening of synapses. On the other hand, usually intrinsic plasticity relies on changes in density or functional properties of voltage-gated ion channels. In response to changing external conditions, cells may adapt plastically to retain function. Titley et al. describe intrinsic plasticity as “cell-autonomous modulation of neuronal excitability” that “modulates the activity level and output efficacy of the entire neuron rather than selected subsets of its inputs” (Titley, Brunel, and Hansel 2017). In response to DBS, strengthening of synapses via LTP due to HF current undoes the lack of current reaching cortical regions in disease state, thus eliminating cortical hypoexcitability. Regaining cortical function demonstrates synaptic plasticity in PD recovery due to DBS (Buonomano and Merzenich 1998).

         Additionally, TMS studies demonstrate motor function in patients and motor cortex plasticity due to STN DBS. Park et al. found that motor evoked potentials with TMS indicate disease state in PD (Park et al. 2016). Kim et al. report normalization of cortical plasticity after STN stimulation paired with dopaminergic medication, but not with just stimulation (Kim et al. 2015). Plasticity evoked through stimulation ended when stimulation was turned off or within an hour subsequent. Cunic et al. report normalization of short-interval intracortical inhibition no change in silent period duration and long-interval intracortical inhibition (Cunic et al. 2002). The authors hypothesize that STN DBS alters only cortical inhibitory circuits because only SICI was changed. Dopaminergic drugs affect SP even in healthy individuals and study participants only had abnormal SICI which may not reflect the entire population of PD. STN DBS may target inhibitory circuits, whereas dopaminergic medication effects dopaminergic pathways. The authors also observed a difference between GPi and STN stimulation, suggesting that these effect different inhibitory cortical circuits with medication. Finally, Goodwill, et al. elaborate on stimulation parameters’ effect on function (Goodwill et al. 2017). “High-frequency rTMS (greater than 5 Hz) and anodal-tDCS typically increase cortical excitability whilst low-frequency rTMS (less than 1 Hz) and cathodal-tDCS result in the opposite effect.” Clinicians set stimulation parameters individually for PD DBS patients, suggesting variability in plasticity.

(Khanna and Carmena 2015)Fig1

(Schmidt and Berke 2017)Fig1

(Petter et al. 2016)Fig

Neuronal inhibition and synaptic plasticity of basal ganglia neurons in Parkinson’s disease Luka Milosevic

# Discusssion

# References

Przedborski, Serge. 2017. “The Two-Century Journey of Parkinson Disease Research”. *Nature Reviews Neuroscience* 18 (4). Springer Nature: 251–59. doi:10.1038/nrn.2017.25.

Kuramoto, L, J Cragg, R Nandhagopal, E Mak, V Sossi, la Fuente-Fernández R de, AJ Stoessl, and M Schulzer. 2013. “The Nature of Progression in Parkinson’s Disease: an Application of Non-Linear, Multivariate, Longitudinal Random Effects Modelling.”. *PLoS One* 8: e76595.

Nandhagopal, Ramachandiran, Lisa Kuramoto, Michael Schulzer, Edwin Mak, Jacqueline Cragg, Jess McKenzie, Siobhan McCormick, et al. 2011. “Longitudinal Evolution of Compensatory Changes in Striatal Dopamine Processing in Parkinsons Disease”. *Brain* 134 (11). Oxford University Press (OUP): 3290–98. doi:10.1093/brain/awr233.

Castrioto, Anna. 2011. “Ten-Year Outcome of Subthalamic Stimulation in Parkinson Disease”. *Archives of Neurology* 68 (12). American Medical Association (AMA): 1550. doi:10.1001/archneurol.2011.182.

Zigmond, MJ, ED Abercrombie, TW Berger, AA Grace, and EM Stricker. 1990. “Compensations after Lesions of Central Dopaminergic Neurons: Some Clinical and Basic Implications.”. *Trends Neurosci* 13: 290–96.

Blesa, J, I Trigo-Damas, M Dileone, Rey NL Del, LF Hernandez, and JA Obeso. 2017. “Compensatory Mechanisms in Parkinson’s Disease: Circuits Adaptations and Role in Disease Modification.”. *Exp Neurol* 298: 148–61.

Brunenberg, Ellen J. L., Pim Moeskops, Walter H. Backes, Claudio Pollo, Leila Cammoun, Anna Vilanova, Marcus L. F. Janssen, et al. 2012. “Structural and Resting State Functional Connectivity of the Subthalamic Nucleus: Identification of Motor STN Parts and the Hyperdirect Pathway”. Edited by Tianzi Jiang. *PLoS ONE* 7 (6). Public Library of Science (PLoS): e39061. doi:10.1371/journal.pone.0039061.

Bell, Peter T., Moran Gilat, Claire OCallaghan, David A. Copland, Michael J. Frank, Simon J.G. Lewis, and James M. Shine. 2014. “Dopaminergic Basis for Impairments in Functional Connectivity across Subdivisions of the Striatum in Parkinsons Disease”. *Human Brain Mapping* 36 (4). Wiley-Blackwell: 1278–91. doi:10.1002/hbm.22701.

Shepherd, Gordon M. G. 2013. “Corticostriatal Connectivity and Its Role in Disease”. *Nature Reviews Neuroscience* 14 (4). Springer Nature: 278–91. doi:10.1038/nrn3469.

Li, Qian, Ya Ke, Danny C.W. Chan, Zhong-Ming Qian, Ken K.L. Yung, Ho Ko, Gordon W. Arbuthnott, and Wing-Ho Yung. 2012. “Therapeutic Deep Brain Stimulation in Parkinsonian Rats Directly Influences Motor Cortex”. *Neuron* 76 (5). Elsevier BV: 1030–41. doi:10.1016/j.neuron.2012.09.032.

Devergnas, Annaelle, and Thomas Wichmann. 2011. “Cortical Potentials Evoked by Deep Brain Stimulation in the Subthalamic Area”. *Frontiers in Systems Neuroscience* 5. Frontiers Media SA. doi:10.3389/fnsys.2011.00030.

Yau, Yvonne H. C., Yashar Zeighami, Travis Baker, Kevin Larcher, Uku Vainik, Mahsa Dadar, Vladimir Fonov, et al. 2017. “Network Connectivity Determines Cortical Thinning In Early Parkinsons Disease Progression”, June. Cold Spring Harbor Laboratory. doi:10.1101/147611.

Horn, Andreas, Martin Reich, Johannes Vorwerk, Ningfei Li, Gregor Wenzel, Qianqian Fang, Tanja Schmitz-Hübsch, et al. 2017. “Connectivity Predicts Deep Brain Stimulation Outcome in Parkinson Disease”. *Annals of Neurology* 82 (1). Wiley-Blackwell: 67–78. doi:10.1002/ana.24974.

Muthuraman, Muthuraman, Günther Deuschl, Nabin Koirala, Christian Riedel, Jens Volkmann, and Sergiu Groppa. 2017. “Effects of DBS in Parkinsonian Patients Depend on the Structural Integrity of Frontal Cortex”. *Scientific Reports* 7 (March). Springer Nature: 43571. doi:10.1038/srep43571.

Baudrexel, Simon, Torsten Witte, Carola Seifried, Frederic von Wegner, Florian Beissner, Johannes C. Klein, Helmuth Steinmetz, Ralf Deichmann, Jochen Roeper, and Rüdiger Hilker. 2011. “Resting State FMRI Reveals Increased Subthalamic NucleusMotor Cortex Connectivity in Parkinsons Disease”. *NeuroImage* 55 (4). Elsevier BV: 1728–38. doi:10.1016/j.neuroimage.2011.01.017.

Tucker, Don M., and Peter A. Williamson. 1984. “Asymmetric Neural Control Systems in Human Self-Regulation.”. *Psychological Review* 91 (2). American Psychological Association (APA): 185–215. doi:10.1037/0033-295x.91.2.185.

Glick, Stanley D., David Alan Ross, and Lindsay B. Hough. 1982. “Lateral Asymmetry of Neurotransmitters in Human Brain”. *Brain Research* 234 (1). Elsevier BV: 53–63. doi:10.1016/0006-8993(82)90472-3.

Cabeza, Roberto. 2002. “Hemispheric Asymmetry Reduction in Older Adults: The HAROLD Model.”. *Psychology and Aging* 17 (1). American Psychological Association (APA): 85–100. doi:10.1037/0882-7974.17.1.85.

Cabeza, Roberto, Nicole D. Anderson, Jill K. Locantore, and Anthony R. McIntosh. 2002. “Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults”. *NeuroImage* 17 (3). Elsevier BV: 1394–1402. doi:10.1006/nimg.2002.1280.

Mehanna, Raja, Jawad A. Bajwa, Hubert Fernandez, and Aparna Ashutosh Wagle Shukla. 2017. “Cognitive Impact of Deep Brain Stimulation on Parkinson’s Disease Patients”. *Parkinsons Disease* 2017. Hindawi Limited: 1–15. doi:10.1155/2017/3085140.

Combs, Hannah L., Bradley S. Folley, David T. R. Berry, Suzanne C. Segerstrom, Dong Y. Han, Amelia J. Anderson-Mooney, Brittany D. Walls, and Craig van Horne. 2015. “Cognition and Depression Following Deep Brain Stimulation of the Subthalamic Nucleus and Globus Pallidus Pars Internus in Parkinson’s Disease: A Meta-Analysis”. *Neuropsychology Review* 25 (4). Springer Nature: 439–54. doi:10.1007/s11065-015-9302-0.

van Hartevelt, Tim J., Joana Cabral, Gustavo Deco, Arne Møller, Alexander L. Green, Tipu Z. Aziz, and Morten L. Kringelbach. 2014. “Neural Plasticity in Human Brain Connectivity: The Effects of Long Term Deep Brain Stimulation of the Subthalamic Nucleus in Parkinson’s Disease”. Edited by David I. Finkelstein. *PLoS ONE* 9 (1). Public Library of Science (PLoS): e86496. doi:10.1371/journal.pone.0086496.

Saenger, Victor M, Joshua Kahan, Tom Foltynie, Karl Friston, Tipu Z Aziz, Alexander L Green, Tim J van Hartevelt, et al. 2016. “Uncovering the Underlying Mechanisms and Whole-Brain Dynamics of Therapeutic Deep Brain Stimulation for Parkinsons Disease”, October. Cold Spring Harbor Laboratory. doi:10.1101/083162.

Kringelbach, ML, AL Green, and TZ Aziz. 2011. “Balancing the Brain: Resting State Networks and Deep Brain Stimulation.”. *Front Integr Neurosci* 5: 8.

Dembrow, Nikolai, and Daniel Johnston. 2014. “Subcircuit-Specific Neuromodulation in the Prefrontal Cortex”. *Frontiers in Neural Circuits* 8 (June). Frontiers Media SA. doi:10.3389/fncir.2014.00054.

Kahan, J, M Urner, R Moran, G Flandin, A Marreiros, L Mancini, M White, et al. 2014. “Resting State Functional MRI in Parkinson’s Disease: the Impact of Deep Brain Stimulation on ’Effective’ Connectivity.”. *Brain* 137: 1130–44.

Hammond, Constance, Hagai Bergman, and Peter Brown. 2007. “Pathological Synchronization in Parkinsons Disease: Networks Models and Treatments”. *Trends in Neurosciences* 30 (7). Elsevier BV: 357–64. doi:10.1016/j.tins.2007.05.004.

Jha, Ashwani, Peter Brown, Alvaro Pascual-Leone, Vilayanur Ramachandran, Jonathan Cole, Sergio Della Sala, Tom Manly, Andrew Mayes, and Oliver Sacks. n.d. “Paradoxes in Parkinsons Disease and Other Movement Disorders”. In *The Paradoxical Brain*, edited by Narinder Kapur, 189–203. Cambridge University Press. doi:10.1017/cbo9780511978098.012.

CHEN, C, V LITVAK, T GILBERTSON, A KUHN, C LU, S LEE, C TSAI, S TISCH, P LIMOUSIN, and M HARIZ. 2007. “Excessive Synchronization of Basal Ganglia Neurons at 20 Hz Slows Movement in Parkinsons Disease”. *Experimental Neurology* 205 (1). Elsevier BV: 214–21. doi:10.1016/j.expneurol.2007.01.027.

Bowyer, Susan M. 2016. “Coherence a Measure of the Brain Networks: Past and Present”. *Neuropsychiatric Electrophysiology* 2 (1). Springer Nature. doi:10.1186/s40810-015-0015-7.

*Cortico-Cortical Communication Dynamics*. 2014. Frontiers Media SA. doi:10.3389/978-2-88919-288-5.

Faisal, A. Aldo, Luc P. J. Selen, and Daniel M. Wolpert. 2008. “Noise in the Nervous System”. *Nature Reviews Neuroscience* 9 (4). Springer Nature: 292–303. doi:10.1038/nrn2258.

Deco, G., V. Jirsa, A. R. McIntosh, O. Sporns, and R. Kotter. 2009. “Key Role of Coupling Delay, and Noise in Resting Brain Fluctuations”. *Proceedings of the National Academy of Sciences* 106 (25). Proceedings of the National Academy of Sciences: 10302–7. doi:10.1073/pnas.0901831106.

Muthuraman, Muthuraman, Günther Deuschl, Nabin Koirala, Christian Riedel, Jens Volkmann, and Sergiu Groppa. 2017. “Effects of DBS in Parkinsonian Patients Depend on the Structural Integrity of Frontal Cortex”. *Scientific Reports* 7 (March). Springer Nature: 43571. doi:10.1038/srep43571.

Krause, Beatrix, and Roi Cohen Kadosh. 2014. “Not All Brains Are Created Equal: the Relevance of Individual Differences in Responsiveness to Transcranial Electrical Stimulation”. *Frontiers in Systems Neuroscience* 8. Frontiers Media SA. doi:10.3389/fnsys.2014.00025.

Groppa, Sergiu, Nicole Werner-Petroll, Alexander Münchau, Günther Deuschl, Matthew F.S. Ruschworth, and Hartwig R. Siebner. 2012. “A Novel Dual-Site Transcranial Magnetic Stimulation Paradigm to Probe Fast Facilitatory Inputs from Ipsilateral Dorsal Premotor Cortex to Primary Motor Cortex”. *NeuroImage* 62 (1). Elsevier BV: 500–509. doi:10.1016/j.neuroimage.2012.05.023.

COSTA, R. M. 2007. “Plastic Corticostriatal Circuits for Action Learning: Whats Dopamine Got to Do with It?”. *Annals of the New York Academy of Sciences* 1104 (1). Wiley-Blackwell: 172–91. doi:10.1196/annals.1390.015.

Shen, W., M. Flajolet, P. Greengard, and D. J. Surmeier. 2008. “Dichotomous Dopaminergic Control of Striatal Synaptic Plasticity”. *Science* 321 (5890). American Association for the Advancement of Science (AAAS): 848–51. doi:10.1126/science.1160575.

Quraishi, S.A., and C.A. Paladini. 2017. “Plasticity in Dopamine Neurons”. In *Handbook of Behavioral Neuroscience*, 361–72. Elsevier. doi:10.1016/b978-0-12-802206-1.00018-0.

Azdad, Karima, Marcelo Chàvez, Patrick Don Bischop, Pim Wetzelaer, Bart Marescau, Peter Paul De Deyn, David Gall, and Serge N. Schiffmann. 2009. “Homeostatic Plasticity of Striatal Neurons Intrinsic Excitability Following Dopamine Depletion”. Edited by Katrina Gwinn. *PLoS ONE* 4 (9). Public Library of Science (PLoS): e6908. doi:10.1371/journal.pone.0006908.

Pascual-Leone, Alvaro, Amir Amedi, Felipe Fregni, and Lotfi B. Merabet. 2005. “THE PLASTIC HUMAN BRAIN CORTEX”. *Annual Review of Neuroscience* 28 (1). Annual Reviews: 377–401. doi:10.1146/annurev.neuro.27.070203.144216.

Temel, Yasin, Veerle Visser-Vandewalle, Süleyman Kaplan, Ramazan Kozan, Marc A.R.C. Daemen, Arjan Blokland, Christoph Schmitz, and Harry W.M. Steinbusch. 2006. “Protection of Nigral Cell Death by Bilateral Subthalamic Nucleus Stimulation”. *Brain Research* 1120 (1). Elsevier BV: 100–105. doi:10.1016/j.brainres.2006.08.082.

Kerschensteiner, Daniel. 2013. “Spontaneous Network Activity and Synaptic Development”. *The Neuroscientist* 20 (3). SAGE Publications: 272–90. doi:10.1177/1073858413510044.

Fox, MD, and ME Raichle. 2007. “Spontaneous Fluctuations in Brain Activity Observed with Functional Magnetic Resonance Imaging.”. *Nat Rev Neurosci* 8: 700–711.

Bach-y-Rita, Paul. 1990. “Brain Plasticity as a Basis for Recovery of Function in Humans”. *Neuropsychologia* 28 (6). Elsevier BV: 547–54. doi:10.1016/0028-3932(90)90033-k.

Frackowiak, RS, P Dowsey-Limousin, M Jahanshahi, and M Hariz. 2003. “[Brain Imaging and Mobility in Parkinson’s Disease].”. *Bull Acad Natl Med* 187: 295–304.

Rascol, O. 1998. “Cortical Motor Overactivation in Parkinsonian Patients with L-Dopa- Induced Peak-Dose Dyskinesia”. *Brain* 121 (3). Oxford University Press (OUP): 527–33. doi:10.1093/brain/121.3.527.

Koch, G., L. Brusa, C. Caltagirone, A. Peppe, M. Oliveri, P. Stanzione, and D. Centonze. 2005. “RTMS of Supplementary Motor Area Modulates Therapy-Induced Dyskinesias in Parkinson Disease”. *Neurology* 65 (4). Ovid Technologies (Wolters Kluwer Health): 623–25. doi:10.1212/01.wnl.0000172861.36430.95.

Fraix, Valérie, Pierre Pollak, Laurent Vercueil, Alim-Louis Benabid, and François Mauguière. 2008. “Effects of Subthalamic Nucleus Stimulation on Motor Cortex Excitability in Parkinson’s Disease”. *Clinical Neurophysiology* 119 (11). Elsevier BV: 2513–18. doi:10.1016/j.clinph.2008.07.217.

Goldberg, Elkhonon. 2002. *The Executive Brain: Frontal Lobes and the Civilized Mind*. Oxford University Press, USA.

Beck, Heinz, and Yoel Yaari. 2008. “Plasticity of Intrinsic Neuronal Properties in CNS Disorders”. *Nature Reviews Neuroscience* 9 (5). Springer Nature: 357–69. doi:10.1038/nrn2371.

Camp, Aaron J. 2012. “Intrinsic Neuronal Excitability: A Role in Homeostasis and Disease”. *Frontiers in Neurology* 3. Frontiers Media SA. doi:10.3389/fneur.2012.00050.

Zhang, Wei, and David J. Linden. 2003. “The Other Side of the Engram: Experience-Driven Changes in Neuronal Intrinsic Excitability”. *Nature Reviews Neuroscience* 4 (11). Springer Nature: 885–900. doi:10.1038/nrn1248.

Titley, Heather K., Nicolas Brunel, and Christian Hansel. 2017. “Toward a Neurocentric View of Learning”. *Neuron* 95 (1). Elsevier BV: 19–32. doi:10.1016/j.neuron.2017.05.021.

Buonomano, Dean V., and Michael M. Merzenich. 1998. “CORTICAL PLASTICITY: From Synapses to Maps”. *Annual Review of Neuroscience* 21 (1). Annual Reviews: 149–86. doi:10.1146/annurev.neuro.21.1.149.

Park, Jaechan, Won Hyuk Chang, Jin Whan Cho, Jinyoung Youn, Yun Kwan Kim, Sun Woong Kim, and Yun-Hee Kim. 2016. “Usefulness of Transcranial Magnetic Stimulation to Assess Motor Function in Patients With Parkinsonism”. *Annals of Rehabilitation Medicine* 40 (1). Korean Academy of Rehabilitation Medicine (KAMJE): 81. doi:10.5535/arm.2016.40.1.81.

Kim, Sang Jin, Kaviraja Udupa, Zhen Ni, Elena Moro, Carolyn Gunraj, Filomena Mazzella, Andres M. Lozano, Mojgan Hodaie, Anthony E. Lang, and Robert Chen. 2015. “Effects of Subthalamic Nucleus Stimulation on Motor Cortex Plasticity in Parkinson Disease”. *Neurology* 85 (5). Ovid Technologies (Wolters Kluwer Health): 425–32. doi:10.1212/wnl.0000000000001806.

Cunic, D., L. Roshan, F. I. Khan, A. M. Lozano, A. E. Lang, and R. Chen. 2002. “Effects of Subthalamic Nucleus Stimulation on Motor Cortex Excitability in Parkinsons Disease”. *Neurology* 58 (11). Ovid Technologies (Wolters Kluwer Health): 1665–72. doi:10.1212/wnl.58.11.1665.

Goodwill, Alicia M., Jarrad A. G. Lum, Ashlee M. Hendy, Makii Muthalib, Liam Johnson, Natalia Albein-Urios, and Wei-Peng Teo. 2017. “Using Non-Invasive Transcranial Stimulation to Improve Motor and Cognitive Function in Parkinson’s Disease: a Systematic Review and Meta-Analysis”. *Scientific Reports* 7 (1). Springer Nature. doi:10.1038/s41598-017-13260-z.

Khanna, Preeya, and Jose M Carmena. 2015. “Neural Oscillations: Beta Band Activity across Motor Networks”. *Current Opinion in Neurobiology* 32 (June). Elsevier BV: 60–67. doi:10.1016/j.conb.2014.11.010.

Schmidt, Robert, and Joshua D. Berke. 2017. “A Pause-Then-Cancel Model of Stopping: Evidence from Basal Ganglia Neurophysiology”. *Philosophical Transactions of the Royal Society B: Biological Sciences* 372 (1718). The Royal Society: 20160202. doi:10.1098/rstb.2016.0202.

Petter, Elijah A., Nicholas A. Lusk, Germund Hesslow, and Warren H. Meck. 2016. “Interactive Roles of the Cerebellum and Striatum in Sub-Second and Supra-Second Timing: Support for an Initiation Continuation, Adjustment, and Termination (ICAT) Model of Temporal Processing”. *Neuroscience & Biobehavioral Reviews* 71 (December). Elsevier BV: 739–55. doi:10.1016/j.neubiorev.2016.10.015.