METHODS IN EXPLORING EFFECTIVE CONNECTIVITY: APPLICATIONS IN MRI AND OUR MODEL OF PARKINSON'S DISEASE

By

ROHITH REDDY BOYILLA

_____

A Thesis Submitted to The Honors College

In Partial Fulfillment of the Bachelor's degree
With Honors in

Neuroscience & Cognitive Science

THE UNIVERSITY OF ARIZONA

M A Y 2 0 2 0

Approved by:

_____

Dr. Nan-kuei Chen
Department of Biomedical Engineering

Abstract

Effective connectivity provides information about the influence one brain region has over another, including directionality of influence and whether activation of one region stimulates or inhibits activity in another (Friston 14). Currently, much of our knowledge of brain network effective connectivity comes from animal studies. New ways of analyzing functional magnetic resonance imaging (fMRI) data have allowed for less invasive means for collecting data on human brain network effective connectivity. fMRI techniques in particular are regularly dismissed as only showing correlation, but new statistical modelling methods are able to establish causal relationships between brain region activation. This paper explores some of the current methods we have available for exploring effective connectivity, and some of the possible applications in Parkinson's Disease (PD) treatment. Although the motor pathway, particularly the nigrostriatal pathway, is relatively well established in literature, the effects that dopamine agonists, such as L-DOPA, have on the effective connectivity of the nigrostriatal and mesocortical pathways has not been thoroughly investigated.

Background

Our current understanding of the anatomy of the brain is thorough. We started with primitive ways to understand our brains like dissection and lesion studies. Now tools like MRI, positron emission tomography (PET), electroencephalograms (EEG), and transcranial magnetic stimulation (TMS) have allowed for detailed in vivo anatomical data. However, knowing just the shape of the brain and its regions only gets us so far (Power et al.). To get more at how regional neural activity plays a role in our

behavior, we need to be able to identify if the neural activity inhibitory or excitatory. Is activity in one region causing activity in another? Is there a directionality to the activation?

In order to properly map connections between neurons and brain regions, three main categories are used: anatomical, functional, and effective connectivity. Anatomical connectivity refers to the physical connections between brain regions. Functional connectivity refers to regions of the brain with temporally corresponding activations, usually during a task. Effective connectivity refers to the “influence that one neural system exerts over another” (Friston 14). This means that in order to establish effective connectivity, causality must also be established.

Much of what we currently understand and how we define brain networks is thanks to functional connectivity data from fMRI and PET scan data. A brain network in itself is essentially a map of functional connectivity for specific tasks. Activation is either hemodynamic response, in the case of fMRI, or cellular glucose uptake, in the case of PET scans. At resting state, the most correlated and significant brain activity typically occurs in the default mode network. Giving patients tasks to do during a scan can show what part of the brain is most likely being used to complete the task, based on activations. By showing correlations between the activation of different brain regions during specific tasks, a brain network can be found (Sporns).

Analysis of fMRI data is proving to be more and more useful at tackling the effective connectivity problem. To better understand how we can get so much information out of what is a really strong magnet, it helps to realize that most of the magic behind MRI’s is in the programming. An image is the result only because code

turns the data of varying magnetic perturbations into a pixel with a specific brightness. The reason we are able to get so much information out of very strong magnets is because of how much data about material properties we can extrapolate from a material's behavior in a changing magnetic field. The raw data can be manipulated in many ways to highlight activations with respect to altered conditions. This is why MRI's are actually responsible for several different methodologies in mapping anatomical networks, functional connectivity, and effective connectivity.

Of course, many classic images of the brain can be seen by the use of regular MRI. Two types of MRI pictures are displayed below.

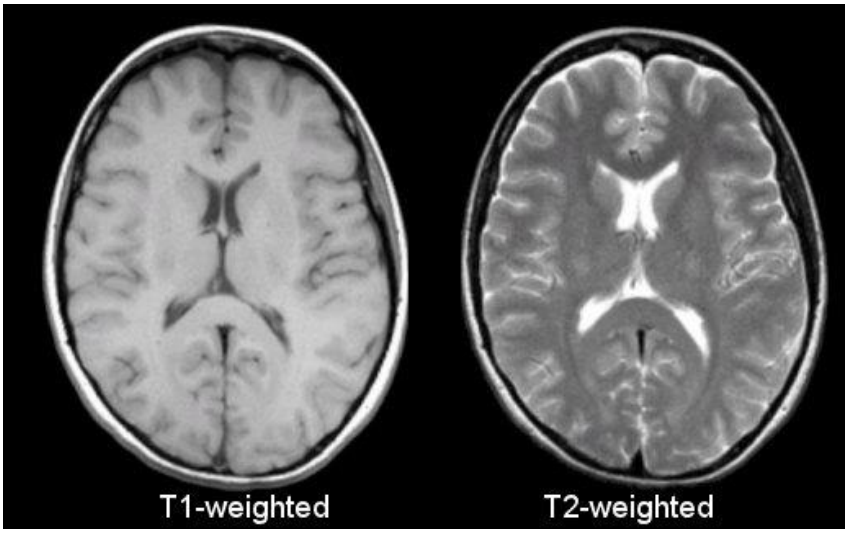

Fig. 1. Two types of MRI imaging.
https://casemed.case.edu/clerkships/neurology/Web%20Neurorad/MRI%20Basics.htm

The contrast and color of different materials can be altered depending on the time constant used to form the images. T1 images make water and CSF seem darker while fat looks brighter. In T2 images, this result is reversed, making CSF seem brighter. A 3D anatomical model can be built by compiling all the different cross section images, so that most of the brain and it's internal regions can be seen in vivo.

However, information on white matter tracts can't be found with just regular T1 or T2 MRI images. On the other hand, diffusion tensor imaging is one MRI method that is able track water diffusion throughout the brain to estimate white matter tract locations and directionality with precision, leading to images like this one:

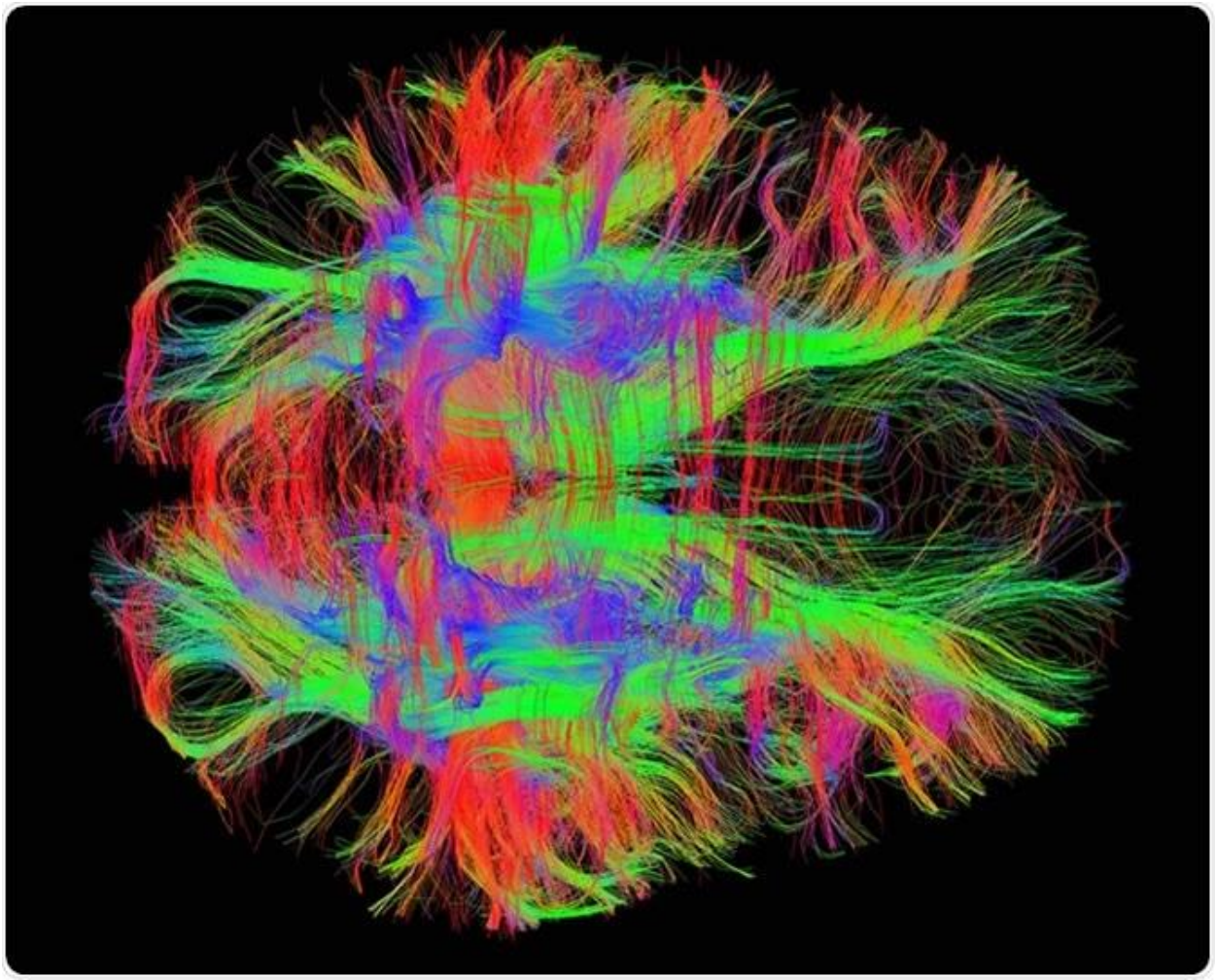

Fig. 2. Zeynep Saygin. Diffusion Tensor Imaging. https://www.news-medical.net/health/Diffusion-Tensor-Imaging-(DTI)-Explained.aspx.

Where each color corresponds to directionality of water diffusion in space. This method of MRI analysis offers high resolution images of white matter tracts. Diffusion tensor imaging provides a great anatomical framework for establishing functional connectivity

and effective connectivity with other methods. After all, functional and effective connectivity are both limited by the brain's anatomical constraints.

When it comes to functional connectivity, the classic example of fMRI is first to the mind. This technique is unique in that it measures the hemodynamic responses, the increased flow of oxygenated blood, in brain regions of interest. fMRI, on its own, can't establish that an event or stimulus causes brain region activity, even if the event or stimulus is given when the subject is in the MRI, but can only show correlations for the interactions between brain regions themselves. However, that's not to say that fMRI can never show causal relationships.

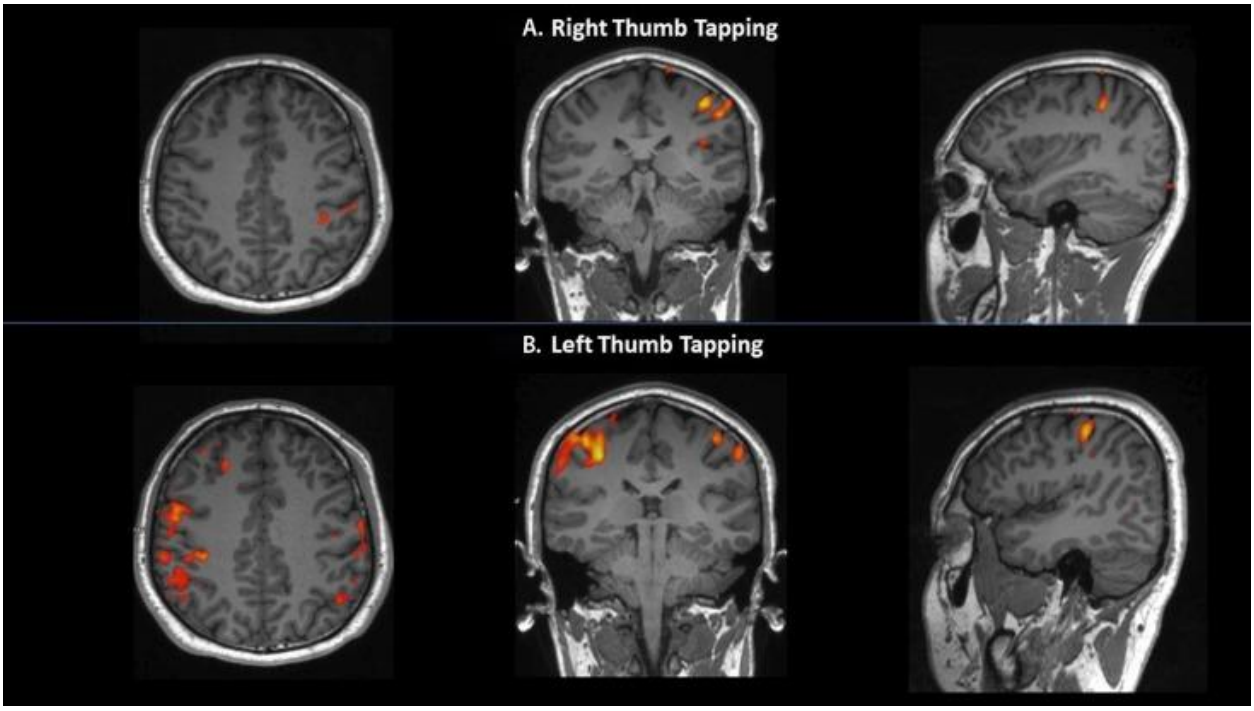

Fig. 3. fMRI image of finger tapping activations. 4 January 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5786990/

PET scans and even optogenetics have proven very helpful in establishing functional connectivity (Lim et al.). Since PET scans can test for brain activity based on regional cellular glucose uptake rather than hemodynamic response, PET scans have a unique

perspective on regional cellular metabolism. This makes it a great tool for detecting problems in tissue function and metabolism, but provides similar data in terms of brain region activations and functional connectivity.

PET and fMRI, by themselves, are only able to show functional connectivity, because they are only showing correlational activations between brain regions. However, it is a common misconception that fMRI can *never* be used to show causal data, and as a result, never show effective connectivity without use of TMS or some kind of direct current stimulation. The logic behind fMRI's inability establishing causal relationships stems from the lack of a clear experimental variable during fMRI studies. With the addition of TMS or direct current stimulation, the added inhibition or stimulation in part of a pathway can act as the experimental variable (Weber et al.). Lesion studies can also be used to simulate inhibition of a brain region (Adolphs). The problem with TMS, direct current stimulation, and lesion studies is that they all carry heavy risks if done on human subjects for non treatment purposes. To circumvent these risks, three main statistical analysis methods are being applied to fMRI and PET scans to establish the most likely directionalities and causalities of activation between brain regions: dynamic causal modeling, structural equation modelling, and granger causality (Friston; Stephan et al.). The basic principle of these is to introduce an experimental variable to fMRI data, by hypothesizing effective connectivity models. Then, a chosen hypothesized model is tested for the probability that it is accurate. This way, the hypothesized model acts as the experimental variable, since the researchers can change it, and then look for how well each hypothesized model fits with the hemodynamic activation patterns (Stephan et al.).

Effective Connectivity Models of Motor System

DeLong started to explore how different parts of the motor pathway change their interactions with each other in the two extreme examples of motor dysregulation: Huntington's and Parkinson's. The study induced something very close to Parkinson's (hypokinetic) in primates by giving them MPTP. MPTP is very selective and lethal for neurons in the substantia nigra (SNr), thus simulating Parkinson's in the primates. In a way, Parkinson's and MPTP are being used like lesion studies to establish causal relationships. In the Hyperkinetic example, a lesion was given to the subthalamic nucleus (STN) to simulate Huntington's. Between the results of the two experiments, in order to explain the results, a working theory of the simplified effective connectivity between the motor network brain regions was developed (DeLong).

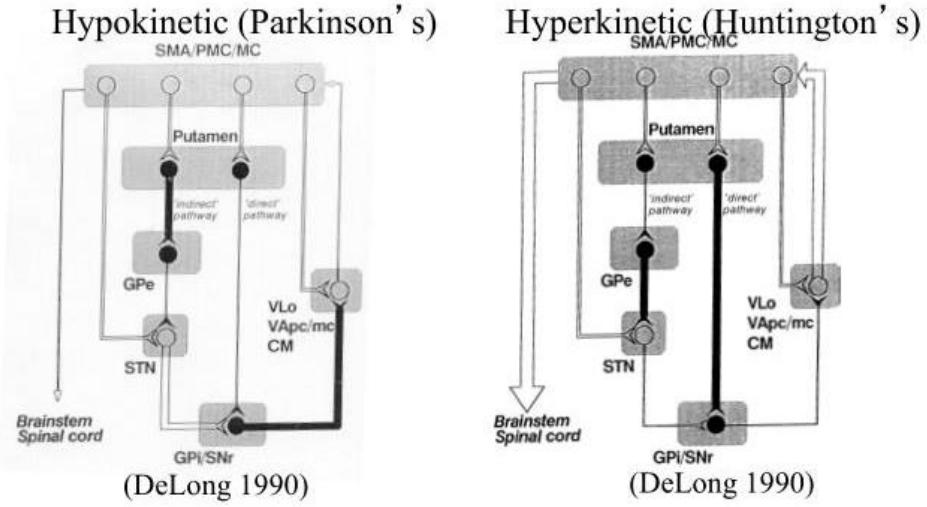

Fig. 4. Simplified effective connectivity models of motor network activity.

The black neurons are inhibitory and the white ones are excitatory. The thickness of the axons corresponds to strength of the signals. Notice how in the hyperkinetic

model, there was increased activation of the direct pathway inhibiting the internal globus pallidus (GPi), which is also an inhibitor, leading downstream to increased brainstem to spinal cord activity (increased movement). On the other hand, the hypokinetic model has increased indirect pathway activity, leading to a release of inhibition STN, stimulating the GPi, an inhibitor, causing overall muscular activity to decrease (DeLong). This model provided a framework for much of our understanding of the motor system today.

In another paper, Grafton et al. introduce the use of structural equation modelling in a human PET scan study. They use DeLong and Alexander's previously shown model to help create their hypothesized starting models to test for statistical fit, as shown in figure 5.

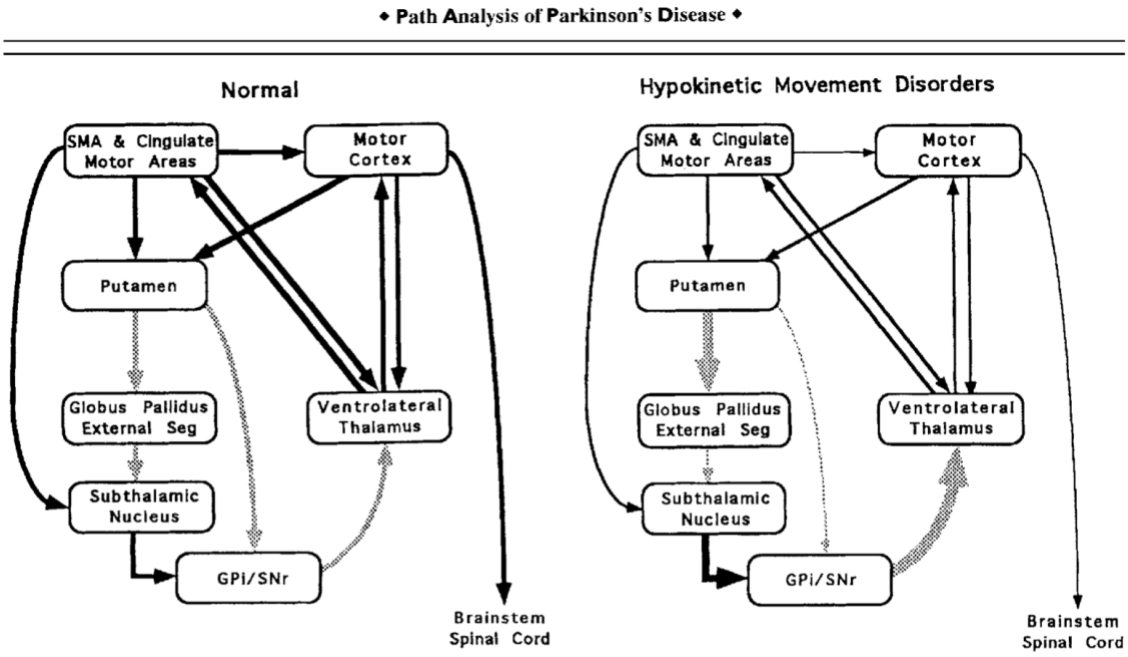

Fig. 5. Grafton et al. These models are based off of the models shown in fig. 4. Shaded arrows correspond to negative activity. Width of arrows correspond to activation strength. Once again, hypokinetic movement disorder marked by increased stimulation in the indirect Putamen pathway.

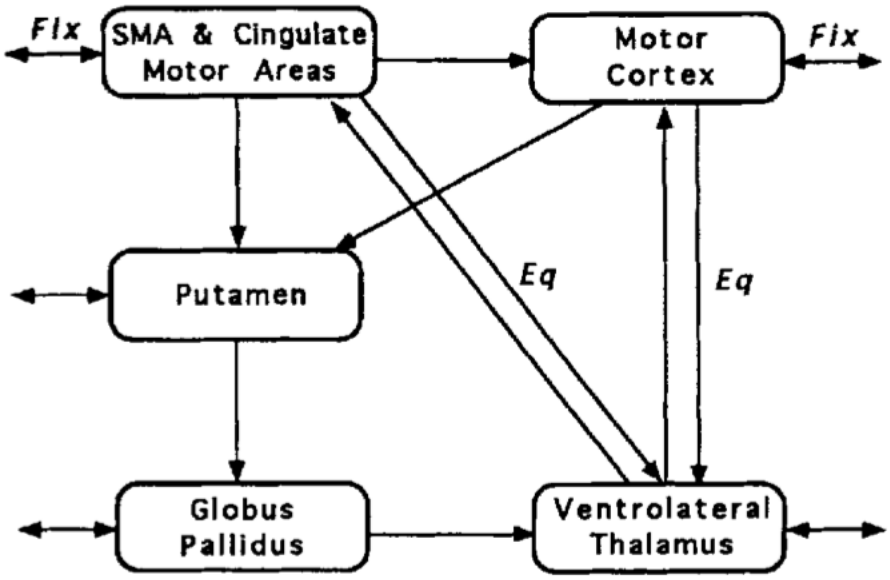

Fig. 6. Grafton et al. model for testing effective connectivity using structural equation modelling technique on PET scans.

They were not able to show some of the regions in the original model in their model because PET couldn't get clear or accurate signals from areas. One significant area that had to be cut is the STN.

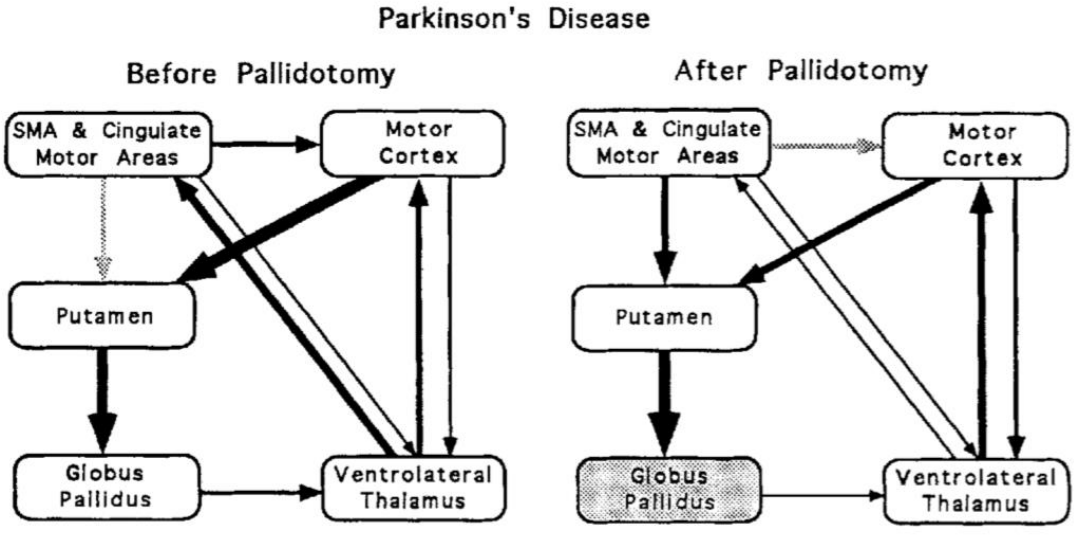

Fig. 7. Grafton et al. Shaded arrows correspond to negative activity. Width of arrows correspond to activation strength. Both are in PD patients during movement.

The study looks at the effects of a pallidotomy on this circuit. They find that, as expected, the remaining bit of the Globus Pallidus after a pallidotomy decreases its output even with the same input from the putamen. The thalamic projection to the SMA/cingulate area is weaker. The other main change is the switch from positive to negative and negative to positive interaction by the SMA (Grafton et al.). The success of pallidotomy may lie in the reintroduction of a negative path to the motor cortex, the lack of which may cause muscle rigidity.

Much is still to be learned from applying these statistical methods to fMRI. Taniwaki et al. explore how the effective connectivity is different for self initiated movement vs externally initiated movement, suggesting there is even more nuance to the models we have been seeing. Figure 7 shows how quickly causal modelling techniques can get complicated. More recently, dynamic causal modelling, and it's application to fMRI, has been growing in popularity. Row et al. began studies on showing the reproducibility of dynamic causal modelling applied to fMRI. They explore the feasibility of fMRI dynamic causal modelling on developing models for Parkinson's and the effects of medication. They conclude that dynamic causal modelling can prove to be a formidable tool, but must be used with caution to avoid misleading results (Rowe et al). Furthermore, the exact nature of how deep brain stimulation contributes to the treatment of Parkinson's has yet to be confirmed. However another study conducts a meta-analysis of PET and fMRI studies to better understand how deep brain stimulation of the STN might change the effective connectivity of the motor network (Chen et al.).

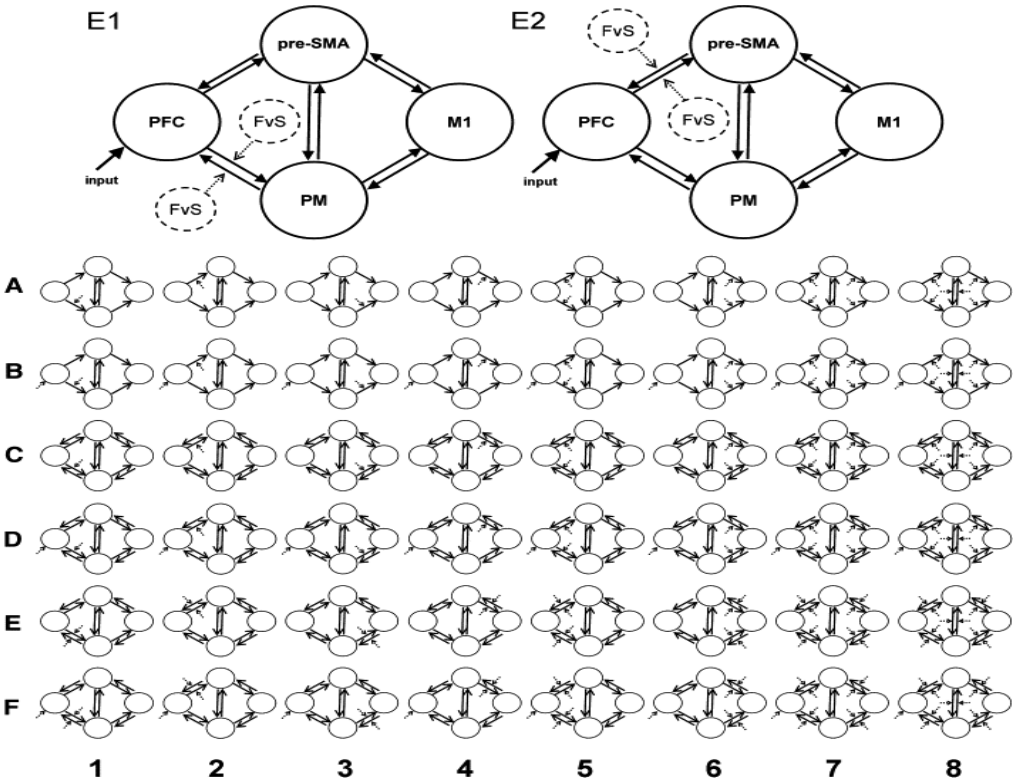

Fig. 7. Rowe et al. Study compares 48 models for fMRI application of dynamic causal modelling to look for best fit.

Applications and Future Directions

This paper itself originated from a need to better understand effective connectivity to properly acquire data on how L-DOPA interacts with the nigrostriatal pathway and mesolimbic pathways. It is understood that dopamine agonist drugs such as L-DOPA are helpful for treating PD, but dopamine agonist treatment can come with the peculiar side effect of increased risk of developing addictive tendencies, particularly to gambling. This is due to the delocalized effects of L-DOPA not only on the nigrostriatal pathway, but also on the mesolimibic and mesocortical pathways, the pathways involved in addiction, reward, and motivation. Interestingly, dopamine levels increase, but mesocortical hemodynamic response activity decreases. It is

hypothesized that prolonged exposure to increased dopamine reduced the dopamine sensitivity of the cells, leading to the resting state decrease in hemodynamic response in the mesocortical areas. Decreased mesocortical activity leads to decreased decision-making capabilities or impulse control. This results in the increased likelihood to develop gambling disorder (Pirritano et al.). However, without application of a statistical model like dynamic causal modelling, there was no feasible way to show whether L-DOPA directly causes increased dopamine levels in the mesolimbic pathway by increasing dopamine production in the VTA, or if the increased dopamine in the nigrostriatal pathway led to decreased mesolimbic/mesocortical activity downstream due to inhibition pathways.

The potential and applications for establishing effective connectivity through fMRI reaches beyond just explaining the gambling side effect. Acquiring or perfecting a code that can compute the probability of a hypothesized effective connectivity given fMRI data as input could streamline effective connectivity model discoveries. Use of statistical causal modeling techniques with fMRI can provide an easily reproducible and low-risk method to acquire effective connectivity data on different networks in the brain. Further contributions can be made to The Human Connectome Project, in efforts to more accurately capture the details that make up the brain (*Human Connectome Project*). Medication/drug activity can be understood more accurately or better localized to particular brain regions of interest. Currently, deep brain stimulation is the most effective treatment for PD patients, but with a better understanding of the effective connectivity of the motor pathway, deep brain stimulation techniques can be better guided for increased accuracy and reduced risk (Chen et al.).

Next steps include improvements on coding for current causal statistics techniques for the fMRI. Development of a more streamlined process to select or design initial models for structural equation model or dynamic causal model testing would standardize the process. Access to more precise region of interest atlases can improve what regions can be included in the models. We can increase research in different networks by moving beyond the motor system to analyze how treatments can affect effective connectivity in diseases besides Parkinson’s.

Works Cited

Adolphs, Ralph. “Human Lesion Studies in the 21st Century.” *Neuron*, U.S. National Library of Medicine, 15 June 2016, www.ncbi.nlm.nih.gov/pmc/articles/PMC5656290/.

Chai, et al. “Exploring EEG Effective Connectivity Network in Estimating Influence of Color on Emotion and Memory.” *Frontiers*, Frontiers, 18 Sept. 2019, www.frontiersin.org/articles/10.3389/fninf.2019.00066/full.

Chen, Hui-Min, et al. “Effective Network of Deep Brain Stimulation of Subthalamic Nucleus with Bimodal Positron Emission Tomography/Functional Magnetic Resonance Imaging in Parkinson's Disease.” *CNS Neuroscience & Therapeutics*, John Wiley and Sons Inc., Feb. 2018, www.ncbi.nlm.nih.gov/pubmed/29222835.

D., Carl, et al. “Resting State Functional Connectivity of the Striatum in Parkinson's Disease.” *OUP Academic*, Oxford University Press, 28 Nov. 2012, academic.oup.com/brain/article/135/12/3699/285680.

DeLong, Mahlon R. “Primate Models of Movement Disorders of Basal Ganglia Origin.” *Trends in Neurosciences*, Elsevier Current Trends, 19 Mar. 2003, www.sciencedirect.com/science/article/pii/016622369090110V.

Duggento, Andrea, et al. “Globally Conditioned Granger Causality in Brain–Brain and Brain–Heart Interactions: a Combined Heart Rate Variability/Ultra-High-Field (7 T) Functional Magnetic Resonance Imaging Study.” *Philosophical Transactions of the*

Royal Society A: Mathematical, Physical and Engineering Sciences, 13 May 2016, royalsocietypublishing.org/doi/full/10.1098/rsta.2015.0185.

Friston KJ. *Functional and Effective Connectivity: A Review*. www.fil.ion.ucl.ac.uk/~karl/Functional%20and%20Effective%20Connectivity%20A%20Review.pdf.

Goldenberg, Diane, and Adriana Galván. “The Use of Functional and Effective Connectivity Techniques to Understand the Developing Brain.” *Developmental Cognitive Neuroscience*, Elsevier, 10 Feb. 2015, www.sciencedirect.com/science/article/pii/S1878929315000250.

Gonen, Tal, et al. “From Animal Model to Human Brain Networking: Dynamic Causal Modeling of Motivational Systems.” *Journal of Neuroscience*, Society for Neuroscience, 23 May 2012, www.jneurosci.org/content/32/21/7218.

Grafton, Scott T., et al. “Network Analysis of Motor System Connectivity in Parkinson's Disease: Modulation of Thalamocortical Interactions after Pallidotomy.” *Wiley Online Library*, John Wiley & Sons, Ltd, 13 Oct. 2004, onlinelibrary.wiley.com/doi/abs/10.1002/hbm.460020106.

Gröger, Adriane, et al. “Dopamine Reduction in the Substantia Nigra of Parkinson's Disease Patients Confirmed by in Vivo Magnetic Resonance Spectroscopic Imaging.” *PloS One*, Public Library of Science, 8 Jan. 2014, www.ncbi.nlm.nih.gov/pmc/articles/PMC3885536/.

Human Connectome Project, USC Mark and Mary Stevens Neuroimaging and Informatics Lab, www.humanconnectomeproject.org/.

Laird, Angela R, et al. “Modeling Motor Connectivity Using TMS/PET and Structural Equation Modeling.” *NeuroImage*, U.S. National Library of Medicine, June 2008, www.ncbi.nlm.nih.gov/pmc/articles/PMC2871686/.

Lebedev, et al. “Large-Scale Resting State Network Correlates of Cognitive Impairment in Parkinson's Disease and Related Dopaminergic Deficits.” *Frontiers*, Frontiers, 11 Mar. 2014, www.frontiersin.org/articles/10.3389/fnsys.2014.00045/full.

Lei, Xu, et al. “Multimodal Functional Network Connectivity: An EEG-FMRI Fusion in Network Space.” *PLOS ONE*, Public Library of Science, journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0024642.

Lewis, M M, et al. “Differential Involvement of Striato- and Cerebello-Thalamo-Cortical Pathways in Tremor- and Akinetic/Rigid-Predominant Parkinson's Disease.” *Neuroscience*, U.S. National Library of Medicine, 17 Mar. 2011, www.ncbi.nlm.nih.gov/pmc/articles/PMC3049982/.

Lim, Diana H, et al. “Optogenetic Approaches for Functional Mouse Brain Mapping.” *Frontiers in Neuroscience*, Frontiers Media S.A., 10 Apr. 2013, www.ncbi.nlm.nih.gov/pmc/articles/PMC3622058/.

Luo, ChunYan, et al. “Reduced Functional Connectivity in Early-Stage Drug-Naive Parkinson's Disease: a Resting-State FMRI Study.” *Neurobiology of Aging*,

Elsevier, 26 Sept. 2013, www.sciencedirect.com/science/article/abs/pii/S0197458013003527.

Ng, Bernard, et al. “Focusing Effects of L-Dopa in Parkinson's Disease.” *Human Brain Mapping*, U.S. National Library of Medicine, Jan. 2010, www.ncbi.nlm.nih.gov/pubmed/19585587.

Perlbarg, Vincent, et al. “Alterations of the Nigrostriatal Pathway in a 6-OHDA Rat Model of Parkinson's Disease Evaluated with Multimodal MRI.” *PLOS ONE*, Public Library of Science, journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0202597.

Pirritano, Domenico, et al. “Gambling Disorder during Dopamine Replacement Treatment in Parkinson's Disease: a Comprehensive Review.” *BioMed Research International*, Hindawi Publishing Corporation, 2014, www.ncbi.nlm.nih.gov/pmc/articles/PMC4119624/.

Power, Jonathan D, et al. “The Development of Human Functional Brain Networks.” *Neuron*, U.S. National Library of Medicine, 9 Sept. 2010, www.ncbi.nlm.nih.gov/pmc/articles/PMC2941973/.

Rowe, J.B., et al. “Dynamic Causal Modelling of Effective Connectivity from FMRI: Are Results Reproducible and Sensitive to Parkinson's Disease and Its Treatment?” *NeuroImage*, Academic Press, 4 Jan. 2010, www.sciencedirect.com/science/article/pii/S105381190901369X.

Sporns, Olaf. “Structure and Function of Complex Brain Networks.” *Dialogues in Clinical Neuroscience*, Les Laboratoires Servier, Sept. 2013, www.ncbi.nlm.nih.gov/pmc/articles/PMC3811098/.

Stephan, Klaas Enno, and Karl J Friston. “Analyzing Effective Connectivity with Functional Magnetic Resonance Imaging.” *Wiley Interdisciplinary Reviews. Cognitive Science*, U.S. National Library of Medicine, May 2010, www.ncbi.nlm.nih.gov/pmc/articles/PMC3013343/.

Taniwaki, Takayuki, et al. “Reappraisal of the Motor Role of Basal Ganglia: a Functional Magnetic Resonance Image Study.” *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience*, Society for Neuroscience, 15 Apr. 2003, www.ncbi.nlm.nih.gov/pmc/articles/PMC6742294/.

Tewari, Alia, et al. “The Striatum and Subthalamic Nucleus as Independent and Collaborative Structures in Motor Control.” *Frontiers in Systems Neuroscience*, Frontiers Media S.A., 1 Mar. 2016, www.ncbi.nlm.nih.gov/pmc/articles/PMC4771745/.

Ventral Striatum - an Overview | *ScienceDirect Topics*. www.sciencedirect.com/topics/neuroscience/ventral-striatum.

Weber, Matthew J, and Sharon L Thompson-Schill. “Functional Neuroimaging Can Support Causal Claims about Brain Function.” *Journal of Cognitive Neuroscience*, U.S. National Library of Medicine, Nov. 2010, www.ncbi.nlm.nih.gov/pmc/articles/PMC3833908/.

Zhang, Delong, et al. “Distinguishing Patients with Parkinson's Disease Subtypes from Normal Controls Based on Functional Network Regional Efficiencies.” *PLOS ONE*, Public Library of Science, journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0115131.

Zhuang, Jiancheng, et al. “Mapping the Connectivity with Structural Equation Modeling in an FMRI Study of Shape-from-Motion Task.” *NeuroImage*, U.S. National Library of Medicine, 15 Aug. 2008, www.ncbi.nlm.nih.gov/pmc/articles/PMC2564811/.